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EDITA IUSSU SOCIETATUM RADIOLOGICARUM
DANIAE, FENNIAE, NORVEGIAE ET SUECIAE

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VOL. 44 SEPTEMBER 1955 Fasc. 3

ACTA RADIOLOGICA

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ACTA RADIOLOGICA
EDITA IUSSU SOCIETATUM RADIOLOGICARUM
DANIAE, FENNIAE, NORVEGIAE ET SUECIAE

VOL. 44 SEPTEMBER 1955 FASC. 3

THE RELIABILITY OF CHOLECYSTOGRAPHY

by

Ingmar G. Wickbom and *Uno Rentzhog*

A lively discussion as to the reliability of the method has ensued since GRAHAM and COLE first described cholecystography in 1924. A great deal has been written on the subject, particularly in the United States, and one of the latest contributions by MORALES and SVEDBERG (1949) was based on 546 cases from Norrköping's Lasarett, Sweden. These authors also reviewed the more extensive of the earlier reports, in most of which the roentgen observations agreed with the operative findings in 90 % to 98 % of the cases. LEVYN's and MEYER's experience was an exception; the findings agreed in only 40 % of their 54 cases. In many of the series published, however, only a small percentage of the abnormal films were ever checked by operation or autopsy. For example, the roentgen observations were interpreted as abnormal in 1,075 of the 2,505 cases of HODGES and LAMPA, yet in only 203 cases, 35 of which showed normal roentgen appearances, were the results confirmed. In 365 of FRIEDMAN's cases, the roentgen examination indicated that the gallbladder was not functioning properly but only 81 of these were submitted to operation.

In these series, little significance was apparently attached to the roentgen findings when deciding for or against operation. Regardless of whether or not this is reasonable, it is impossible to learn the trustworthiness of cholecystography from a material of this kind. The percentage of cases, in which the roentgen and surgical observations agree, does not give much information because for one thing, the figures are dependent upon what is meant by abnormal roentgen or surgical find-

Submitted for publication, 12 February 1955.

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ings. Furthermore, it is a question of two different factors, to some extent independent of one another, firstly, the presence of stones and, secondly, abnormalities of the gallbladder walls and of gallbladder function. Certain authors, *e. g.* OLSSON, and MORALES and SVEDBERG refrain from giving percentages of this kind.

'Poor filling' of the gallbladder is an expression used in most publications, but no author has described precisely what is meant by it. Some say nothing about the technique they use, others only a little. In order to appreciate what poor or no contrast filling signifies, it is necessary to know in what way and how much of the medium was administered, as well as the attention paid to the primary sources of error. For the demonstrations of stones, roentgenograms must in some cases be obtained under fluoroscopic control with the patient erect and the gallbladder compressed. This does not seem to have been done in all the studies and is probably why stones were often found, when the roentgenograms seemed to be normal, as occurred in 5 out of 10 cases in DORAN's series and in 4 out of 5 in COLP's. It is also important to know, in judging the results, what contrast medium was used. Formerly, only preparations containing tetraiodophenolphthalein sodium were used; from now on we shall call all agents containing this substance Cholotrast after the Swedish preparation employed by us. In 1940, the firm of Schering introduced another contrast medium, beta-(4-hydroxy-3,5-diiodophenyl) alpha-phenyl-propionic acid, with the proprietary name of Biliselectan; it is the equivalent of Bilitrast, Priodax, Pheniodol and others. This type of medium seems to have gained in popularity during recent years; agents of this type will be called Bilitrast, after the Swedish preparation we generally used. The more recent type of contrast medium with three atoms of iodine per molecule, *e. g.*, Telepaque, was not available during the period the present study was carried out. As one of us (W.) previously demonstrated, agents of the Bilitrast type result in better visualization of the gallbladder than the former type. Certain authors have used media of the first, and others media of the second group. Still others, like MORALES and SVEDBERG, used both types but did not divide up their material accordingly.

The series published hitherto, therefore, are in several respects unsuitable for judging the value of cholecystography; moreover, many of them contain too few cases. It is, however, of great practical importance to know, to what extent cholecystography may be relied upon to detect disease of the gallbladder. At present, the greatest uncertainty is felt, when the only diagnostic guide is the absence of filling. This is the only sign of abnormality in many cases, usually amounting to 60 % to 70 % (a bare 50 % in OLSSON's cases, however). We have been

fortunate in having access to a large series of cases from Serafimerlasarettet, in which both cholecystography and operation were performed, and which are, therefore, particularly suited for a study of the value of cholecystography. An analysis of this series should be of interest, especially since we are now able to examine the biliary passages roentgenologically after the intravenous administration of the new contrast medium Biligrafin.

The series consists of 1,340 cases from the years 1937 to 1948. During this period, practically every patient with abnormal roentgen appearances was submitted to operation, unless distinct contraindications were present. The series does not include cases in which the roentgen examination was carried out at another hospital, those in which gallstones were an incidental finding in another roentgen examination, or those in which only conventional films were taken. Nor does it include 77 patients operated upon at short notice without any previous examination. Finally, cases were excluded in which more than six months elapsed between the cholecystographic examination and the operation. Up to 1943, preparations containing tetraiodophenolphthalein sodium were used. During the years 1944 and 1945, the two types of contrast medium were used alternately. After 1945, the Bilitrast type of medium was used almost exclusively. Otherwise the same technique, on the whole, was used.

The day before the examination the patient was first given a fatty meal to empty the gallbladder, followed by a double dose of the medium (8 g of Cholotrast or 6 g of Bilitrast). In some cases, the whole dose was administered at 7 p. m., in others, half the dose was given at 2 p. m. and the other half at 7 p. m. The patient was then kept on a light diet, all fats being withheld. The examination was carried out the next morning at 8 a. m. after the patient had been given a large water enema. A preliminary film (24 by 30 cm) with the patient prone was first obtained to see whether the gallbladder was sufficiently filled. If so, further films were made under fluoroscopic control with the patient erect, the gallbladder being compressed and a small diaphragm employed. Whenever no filling was evident, or visualization so poor that the presence or absence of stones was uncertain, the patient was questioned regarding his proper ingestion of the drug and as to any subsequent vomiting or diarrhoea. In the latter event, he was examined again the next day following further dosage and after administration of tincture of opium. Attempts were also made to eliminate every other source of error. In doubtful cases in which there were obvious bowel contents in the region of the gallbladder, the intestine was evacuated, a further preliminary film taken to see whether it was quite clear, and a new series of roentgenograms

obtained of the gallbladder. Other sources of error may be extensive injury to the liver parenchyma, breast-feeding (OLSSON) and pernicious anaemia (LINDQUIST, SOHRNE). The contrast medium must not be retained in the stomach. Should this happen, it is generally detected in the preliminary film. It has also been reported that duodenal ulceration may cause lack of filling (LEB, ORATOR, and others) but, judging from the results of the present study this in not often the case.

The results presented of the cholecystographies are, in the main, those originally recorded. In doubtful cases, however, the films were reviewed by one of us (W.). The operative findings were taken from the records of the operation and the pathologic report upon the gallbladder. As a rule, no attention was paid to the size of the stones, as it had little influence on the decision to operate. The functioning of the gallbladder is dependent for the most part on the condition of its walls. The cases were grouped, therefore, according to the degree of cholecystitis present, the gallbladder being designated either as thick-walled or thin-walled. This grouping was not difficult in the acute cases with severe lesions and distinct inflammation, or in the chronic cases with fibrous thickening of the walls and shrinking of the whole organ. Nor was it difficult in those cases in which the surgeon specifically stated that the gallbladder had thin walls and microscopy showed that the tissue was normal or showed only insignificant lesions. It was not quite so easy, however, when the lesions were slight or moderate. Another obstacle lay in the fact that the length, thoroughness and wording of the account of the operation varied with the surgeon who dictated it. In order to counteract this, however, the surgical and pathologic records were compared, before the cases were grouped. In a few cases, the gallbladder was unfortunately not examined microscopically, and in these, if it was also impossible to judge its condition from the surgeon's account, the case was put in a separate group. It is hard to draw a distinct line between these cases and the thin-walled group and, as a rule, the borderline cases with slight cholecystic lesions were put in the latter group. No attention was paid to adhesions, for these, in our opinion, do not affect the functioning of the gallbladder.

In classifying the cases according to the roentgen observations, we found it most practical first to classify them according to the degree of filling, and then according to whether or not stones were visualized. Each group was divided again into cases examined with Cholotrast and those examined with Bilitrast, in order to see whether the type of contrast agent made any difference. The cases from 1944 and 1945, when both kinds of agents were used, were put into the Bilitrast group because filling was often obtained with Bilitrast, when it was not obtained with Cholotrast; the reverse was never true. During these years, every second

patient was given Cholotrast first and every other Bilitrast first; whenever the gallbladder was not visualized with one medium, the second agent was administered.

In 72 per cent of the 590 cases in which the roentgen examination revealed stones in a contrast-filled gallbladder, slight or no cholecystitis was found on operation. These cases were divided into one group with 'normal' filling and another with poor filling. Table 1 shows the 419 cases in the first group, in which good filling was obtained. In all except 2 of these cases, the roentgen diagnosis was confirmed by the discovery of stones in the gallbladder at operation. In one of the two exceptions, the roentgen examination revealed a normally filled gallbladder and a few grain-sized calcifications. On operation, a thin-walled gallbladder without any stones or adhesions was found, and microscopic analysis revealed a thin-walled gallbladder with sparse round cell infiltration in the stroma. A roentgen examination of the specimen removed, however, showed calcification in the wall, explaining the appearances seen in the cholecystography. In the other exception, the films exhibited a normally filled gallbladder with a calcification the size of a peppercorn. A barium meal examination revealed ulcerous deformity of the duodenal bulb. On operation the wall of the gallbladder was found to be thickened; the lumen of the gallbladder contained normal bile but no stones. The histologic diagnosis was fibrosis of the wall with chronic inflammatory infiltration. The mucous membrane was ironed out in places and showed extensive sloughing of the epithelium. Unfortunately the specimen removed was not examined roentgenographically. Both these cases were from 1944.

Table 1

Cases in which cholecystographic examination showed normal filling and stones

Observations at operation	Cholotrast	Bilitrast	Total
Thickened gallbladder wall and stones	29	54	83
Thin gallbladder wall and stones	98	227	325
No data as to state of gallbladder wall; stones found	4	5	9
Thickened gallbladder wall; no stones	—	1	1
Thin gallbladder wall; no stones (calcification in wall)	—	1	1
	131	288	419

Table 2 covers the 171 cases in which the roentgen films showed poor filling and the presence of stones. (In this article 'poor filling' means that the density of the contrast-filled gallbladder, although definitely lower than the average, is sufficient to reveal or exclude defects caused by calculi.) The latter was confirmed at operation in all instances. The

contrast medium in the gallbladder in these cases, although sufficient to reveal lithiasis, was less concentrated than ordinarily. It was not possible to draw a sharp line between these cases and those showing normal filling, but we made this grouping in order to see, what poor filling signified. The wall of the gallbladder was diseased in 20 per cent of the cases of normal filling and in 35 per cent of the cases of poor filling. This difference is statistically significant. In other words, there is a greater likelihood of disease of the wall when the gallbladder is poorly visualized than when it is well filled. This would indicate that poor filling may sometimes be due to abnormality of the wall. On the other hand, many of the thin-walled gallbladders, 101 in number, were only faintly visualized. In only one of them could this be explained by a stone in the common duct. It appears from this that poor filling by itself, without any signs of stones, is not a reliable criterion of abnormality. If all cases of this kind were operated upon, much unnecessary surgical exploration would be performed.

Table 2

Cases in which cholecystographic examination showed poor filling and stones

Observations at operation	Cholotrast	Bilitrast	Total
Thickened gallbladder wall and stones	23	37	60
Thin gallbladder wall and stones	47	54	101
No data as to state of gallbladder wall; stones found	8	2	10
	78	93	171

When the gallbladder did not fill well, although sufficiently to exclude the presence of stones, the poor filling in itself was not considered abnormal. In 6 cases of this nature, operation was performed because of the strong clinical suggestion of gallstones. In none of these cases stones were found, however, and the wall of the gallbladder only showed slight changes.

Only when the filling was so defective as not to permit the detection of stones was it considered abnormal. In some cases the density was no greater than might have been expected from the gallbladder itself without the presence of any contrast medium. This is the same thing as no filling. The 28 cases in which this happened are shown in Table 3. In 9 of the cases the films also suggested the presence of radio-translucent calculi. Operation disclosed lithiasis in all these cases. Stones were found in 14 of the other 19 cases, but none in the remaining 5. In one of the latter, there was a pea-sized calculus in the common duct and the gallbladder was shrunken and thick-walled. In 3 others, the gallbladder wall

was said to be thickened; a microscopic examination showed marked lesions in one case and moderate lesions in the remaining two cases. In the fifth case of no stones, the gallbladder wall was thin and only slightly infiltrated with round cells, but the whole pancreas was indurated. This patient had diarrhoea after taking the medium, which, as the common duct was of normal width, was probably the main reason for the poor filling.

Table 3

Cases in which cholecystographic examination showed abnormally poor filling

Observations at operation	Cholotrast		Bilitrast		Total
	Probable stone	No stone visible	Probable stone	No stone visible	
Thickened gallbladder wall and stones	2	6	1	2	11
Thin gallbladder wall and stones	2	3	4	2	11
No data as to state of gallbladder wall; stones found	—	1	—	—	1
Thickened gallbladder wall; no stones	—	1	—	3	4
Thin gallbladder; no stones	—	—	—	1	1
	4	11	5	8	28

The gallbladder did not fill at all in 722 cases. Only in 22 per cent of these was there no sign of cholecystitis at operation. The 722 cases were divided into one group of 138 in which stones were visualized, and another of 584 in which they were not. The first group is seen in Table 4. Operation confirmed the presence of stones in all these cases except one. This patient was admitted with pain resembling biliary colic and had been troubled for two or three years with burning pain in the epigastrium, heartburn, and acid belching. The gallbladder did not fill with contrast medium, but a semicircular calcified formation as well as a few small spots of calcification, were seen in the films. On operation, a slightly dilated gallbladder free from stones was found. The common bile duct was greatly dilated and its walls were thickened. The head of the pancreas contained a fairly discrete mass the size of a walnut. Cholangiography demonstrated stricture of the lower part of the common duct, suggesting infiltration by a tumour. It being obvious that partial obstruction was present, cholecystogastrostomy was performed. The diagnosis of chronic pancreatitis with possible malignancy was made. On re-examination of the patient seven years later, the gallbladder still failed to fill, but signs of calcification were no longer visible.

Table 4

Cases in which cholecystographic examination showed no filling but the presence of stones

Observations at operation	Cholotrast	Bilitrast	Total
Thickened gallbladder wall and stones	44	54	98
Thin gallbladder wall and stones	20	15	35
No data as to state of gallbladder wall; stones found	4	—	4
Thin gallbladder wall; no stones	1	—	1
	69	69	138

In the second group in which the gallbladder failed to fill, the lack of filling was the only guide to the diagnosis. This group includes 584 cases (Table 5). In 538 of these, operation disclosed gallstones, but in the remaining 46 it did not. However, in 19 of these 46 cases the wall of the gallbladder was markedly diseased; either it was thickened, indurated and shrunken, highly edematous, or contained areas of hemorrhagic infarction, and pericholecystitic abscesses were present in several cases. Besides these 19 cases, there were 12 cases of distinct but more moderate abnormality of the gallbladder wall, in which it was stated that the wall was thickened, moderately thickened, or showed slight but distinct inflammatory thickening. On microscopic examination, the wall was found to be more or less fibrotic and infiltrated with round cells. In one of these cases cholangiography suggested a small calculus, but this was not confirmed on choledochotomy and instrumental examination. In another case, in which the wall of the gallbladder was thickened and showed marked subchronic infiltration in all its layers, there was severe inflammatory edema around the deep biliary passages. This patient returned three months later with jaundice. The abdomen was opened again and cholangiography performed, but no abnormality was seen. The patient died a few days later. Autopsy revealed carcinoma of the porta hepatis, originating in the hepatic duct. In the remaining 15 out of the 46 cases, 9 of which were examined with Bilitrast and 6 with Cholotrast, the wall of the gallbladder showed at the most only insignificant cholecystitis. In 2 of the Bilitrast cases, the absence of filling may have been due to the fact that the patient had diarrhoea for two days after taking the contrast medium; in one of these, however, cholangiography during operation revealed a dilated common duct. No stones were found by the surgeon, but the dilatation indicated partial obstruction. In another case, the patient probably did not carry out the instructions explicitly. He was first examined in the out-patient department but, when the examination was repeated a few weeks following a negative exploration, the gallbladder filled normally. In another case the patient was admitted for acute pancreatitis. In still another case

the patient also suffered from duodenal ulceration and syphilis. Turning to the 6 cases in which Cholotrast was used, in 3 cases the failure to fill was probably due to impaired liver function. One of these patients was distinctly jaundiced at the time of the examination and in the second case the bilirubin index in the blood rose to 50 two weeks later. In the third case a severely cirrhotic liver was encountered at operation. However, the liver function does not seem to have been tested. In a fourth case the gallbladder was found to be greatly dilated but otherwise normal, and no stones were discovered. The common duct was as thick as a loop of jejunum and contained brown purulent bile. On cholangiography the contrast medium was seen to pass freely into the duodenum. A large amount of granulation tissue from the common duct was suspected by the histologist as coming from a papilloma and three years later the diagnosis was confirmed at autopsy. In the 6 remaining cases, 4 from the Bilitrast and 2 from the Cholotrast series, nothing to explain the lack of filling could be found. It is true that in two instances there were extensive adhesions of omentum around the thin-walled gallbladder, but the wall itself was only slightly diseased. In two cases the examination was carried out in the out-patient department.

Table 5

Cases in which cholecystographic examination showed no filling or stones

Observations at operation	Cholotrast	Bilitrast	Total
Thickened gallbladder wall and stones	171	236	407
Thin gallbladder wall and stones	44	69	113
No data as to state of gallbladder wall; stones found	17	1	18
Thickened gallbladder wall; no stones	21	10	31
Thin gallbladder wall; no stones	6	9	15
	259	325	584

In one of the cases in which the lesions in the wall of the gallbladder were too slight to explain the absence of filling, duodenal ulceration was present. LEB stated that the gallbladder failed to fill in 26 out of 100 cases of duodenal ulcer confirmed by roentgen examination; operation was performed in 10 of these 26, but in no instance was any lesion found in the gallbladder. The gallbladder also failed to fill in 15 out of ORATOR's 25 cases of ulcer, and in all 15 operation disclosed normal appearances; in some of the cases the contrast medium was given intravenously. LEB concluded from a number of animal experiments that the reason why the gallbladder failed to fill in these cases was that it was prevented from emptying by adhesions, and consequently the contrast medium

never entered it. ORATOR, on the other hand, was of the opinion that the hyperacidity associated with ulceration caused a continuous flow of bile into the intestine, with the result that the contrast medium also emptied directly into the duodenum.

Routine roentgen examination of the stomach and duodenum was also carried out before operation in a large number of the present cases. In 59 cases, roentgen evidence of abnormality of the gallbladder was combined with roentgenologic evidence of ulceration. Operation revealed stones in 57 of these cases, in several of which the gallbladder filled with contrast medium, though large, callous duodenal ulcers were present. In the other 2 cases ulcerous deformity of the duodenal bulb was seen in the films but no ulcer. In one of these cases, in which roentgen examination showed an area of calcification the size of a peppercorn in an otherwise normally filled gallbladder, operation disclosed cholecystitis but no stones. Unfortunately the tissue removed was not submitted to roentgen control. In the second case, in which the roentgen examination was performed in the out-patient department, the gallbladder failed to fill; operation revealed a healthy gallbladder and a pea-sized, radiating scar on the anterior aspect of the duodenum close to the pylorus; the duodenal wall was slightly thickened but no ulcer could be palpated. Both cases have been mentioned before.

In our opinion, as long as the correct technique is used, duodenal ulceration is not so often a source of error in cholecystography as reported. However, the chances of it causing defective filling cannot be definitely ruled out.

In Table 6, in which the 1,340 cases with roentgen evidence of abnormality of the gallbladder are collected, it is seen that the most common abnormality was lack of filling, occurring in 56 per cent of the cases. In some of these, however, the films also showed signs of stones, and in only 45 per cent of the whole series was absence of filling the only abnormality. In 552 cases, the only contrast medium used was Cholotrast, and in 788 Bilitrast or both. The gallbladder filled in 48 per cent of the cases in which Bilitrast was used, but in only 38 per cent of those in which Cholotrast was the contrast agent, a difference which is highly significant. It is obvious from these cases, therefore, that the gallbladder fills more often when Bilitrast is employed than when Cholotrast is the contrast medium, or, in other words, that Bilitrast is more likely to reveal lithiasis. When Bilitrast was used, the filling occurred in 92 of the cases in which thickening of the wall was found at operation, or 23 per cent, and did not fill in 306 cases. The corresponding figures for Cholotrast were 52 (17 per cent) and, 245, respectively. On the other hand, when the walls were found to be normal at operation, the gallbladder filled in

Table 6

Review of the 1,340 cases with abnormal cholecystographic features

Observations at operation	Cholotrast	Bilitrast	Total
Gallbladder filled and stones visible			
Thickened gallbladder wall and stones	52	91	143
Thin gallbladder wall and stones	145	281	426
No data as to state of gallbladder; stones found	12	7	19
Thickened gallbladder wall; no stones	—	1	1
Thin gallbladder wall; no stones (calcification in wall)	—	1	1
	209	381	590
No filling of gallbladder with or without stones directly visible			
Thickened gallbladder wall and stones	223	293	516
Thin gallbladder wall and stones	69	90	159
No data as to state of gallbladder; stones found	22	1	23
Thickened gallbladder wall; no stones	22	13	35
Thin gallbladder wall; no stones	7	10	17
	343	407	750
Stones visible with or without filling			
Thickened gallbladder wall and stones	98	146	244
Thin gallbladder wall and stones	167	300	467
No data as to state of gallbladder; stones found	16	7	23
Thickened gallbladder wall; no stones (probable or proved calcification in wall)	—	1	1
Thin gallbladder wall; no stones (probable or proved calcification in wall)	1	1	2
	282	455	737
No stones visible, no filling			
Thickened gallbladder wall and stones	177	238	415
Thin gallbladder wall and stones	47	71	118
No data as to state of gallbladder wall; stones found	18	1	19
Thickened gallbladder wall; no stones	22	13	35
Thin gallbladder wall; no stones	6	10	16
	270	333	603

282 cases (74 per cent) in which Bilitrast was used, and failed to fill in 100 cases. The corresponding figures for Cholotrast were 145 (67 per cent) and 76, respectively. It would appear from this that the gallbladder is more likely to fill with Bilitrast, irrespective of the condition of its wall. The difference is statistically significant. When Bilitrast is used, normal filling thus sometimes occurs even in the presence of slight to moderate cholecystitis but no lithiasis. This has already been pointed out by one of us (W.). We have only two cases to bear this out, however,

for operation was as a rule not performed when normal visualization was obtained, even if there was no filling with Cholotrast. The number of cases with diseased walls of the gallbladder in which the lumen fails to fill, and in which no stones are found at operation, should thus be greater in the Cholotrast than in the Bilitrast series. In 21 of the 35 cases of no filling and no stones in the present series (Table 6), the wall was so changed that it would have been impossible to fill with any contrast medium. Excluding these, we are left with 9 cases in the Cholotrast series, or 3.3 per cent, and 5 cases in the Bilitrast series, or 1.5 per cent, of disease of the gallbladder wall but no stones. The difference is not statistically significant. It may be concluded, therefore, that cholecystitis of a moderate degree is seldom present, if normal roentgen appearances are obtained with Bilitrast.

In 25 cases, operation was performed despite apparently normal observations on roentgen examination. In 3 of the cases, the patient was a parathyfoid carrier. In the other cases, however, the clinical manifestations so strongly suggested biliary disease that the negative roentgen findings were disregarded. In 21 cases, the gallbladder appeared normal on operation. In 4 cases, however, 2 from the Cholotrast and 2 from the Bilitrast series, stones were found. One of these patients had twice undergone roentgen examinations with an interval of seven months between each; the observations were reported as normal although there was evidence suggesting a small calculus on the second occasion. On laparotomy after the second examination, the gallbladder appeared normal to palpation. A further operation four months later, however, revealed a stone the size of a small pea. In another case, a stone of the same size as well as a smaller stone were found and, in a third, about ten stones the size of hazel-nuts and smaller. The reason that these stones were not visualized in the filled gallbladder must have been either that they were so loosely packed that the contrast medium was able to penetrate between the flakes of cholesterol or that they were as radio-opaque as the former. In a later case in which roentgen examination on several occasions showed no definite signs of lithiasis, operation disclosed several pea-sized cholesterol calculi which, when dried, broke down into an amorphous mass. The last films obtained, however, exhibited a number of faint defects in the filling.

In 10.9 per cent of the entire series, operation disclosed a stone in the common duct. A calculus was present in the duct in 5.1 per cent of the cases in which roentgen examination showed filling of the gallbladder and stones, and in 15.5 per cent of the cases in which the gallbladder failed to fill.

Since the investigation of this series, a new intravenous preparation

of the name of Biligrafin (Schering) has appeared on the market. When the liver functions normally, this substance is excreted in such a strong concentration that it is also visualized in the biliary ducts, making their study possible even when the gallbladder has been removed. As far as the examination of the gallbladder is concerned, this contrast medium possesses the advantage in making the reason of lack of filling more easy to determine. If the biliary ducts but not the gallbladder fill with the medium, there must be an obstacle to the flow of bile into the cystic duct or gallbladder, consisting either of stones or of lesions in the walls. It is then possible to eliminate errors such as faulty absorption by the intestine or reduced liver function. Examination with this agent is, however, more complicated and time-consuming than with the substances given by mouth. Moreover, it does not mix so well with the bile in the initial stages and defects in the contrast filling may be erroneously interpreted as calculi. The mixing improves after a while, especially if the patient is given a fatty meal, but this means spreading the examination out over an even greater length of time. Excellent filling may be obtained with this substance even when the wall of the gallbladder is severely damaged and takes up only a small amount of water. The result is that it is more difficult to judge the condition of the walls than when the orally administered media are used. In our opinion, therefore, the latter type of contrast medium will continue to be the most suitable one for routine work, although it may sometimes be advantageous to carry out examinations with Biligrafin as well. We hope that the results of our investigation will help to show in which cases it should be used as an adjunct.

Conclusions

Whenever roentgen examination of the gallbladder points to gallstones, either directly, or indirectly as defects in its contrast-filled lumen, the evidence may be relied upon almost completely. If there is any calcification in the walls of the gallbladder it may be difficult to distinguish this from lithiasis; the difficulty seldom occurs in practice.

Failure of the gallbladder to fill with contrast medium is almost conclusive evidence that it is diseased, provided the correct technique, especially as regards the ingestion of the medium, is employed. The patient must be asked carefully whether he vomited or had diarrhoea after the administration. Caution must be observed when judging the results of roentgen examinations performed on out-patients, who are not observed as closely as others. Extensive injury to the liver parenchyma must be excluded, and it must be remembered that incipient hepatitis

may prevent the gallbladder from filling before any sign of jaundice has developed. Other sources of error are retention of the contrast medium in the stomach, pernicious anaemia and breast-feeding. Likewise, other abnormal conditions in the biliary passages or adjacent tissues, especially tumours of the gallbladder, biliary ducts, or head of the pancreas, may cause defective filling. Duodenal ulceration may occasionally have the same effect.

If the filling is so poor that it is impossible to state definitely whether or not stones are present, the result may be considered the same as no filling. If the filling is poor, but sufficient to indicate or exclude lithiasis, it need not be considered abnormal. However, if Bilitrast has been given, the poor filling may sometimes denote disease of the walls of the gallbladder.

Bilitrast is more likely than Cholotrast to lead to filling of the gallbladder, regardless of whether or not its walls are diseased. Therefore, there is a better chance of visualizing stones directly when Bilitrast is used.

In three-quarters of our cases in which the gallbladder failed to fill the walls were diseased. However, changes in the walls were present in only one quarter of the cases in which stones were seen in a contrast-filled gallbladder. A normal cholecystographic finding practically always excludes disease of the gallbladder, but exceptions may occur. Collections of cholesterol flakes may be present which can form stones. A strong clinical suggestion of gallbladder disease may therefore occasionally warrant a surgical exploration, provided all other conditions are first carefully eliminated.

SUMMARY

The reliability of oral cholecystography is studied in 1,340 cases from Serafimerlasarettet during the years 1937 to 1948. During this period only a few cases were operated upon without a preceding roentgen examination and practically every case in which the cholecystographic observations were interpreted as abnormal were subjected to operation. The results of the study indicate that the method is extremely reliable. The significance of poor filling and the sources of error are discussed. The intravenous contrast medium, Biligrafin, had not been placed on the market at the time of these cases. It is hoped that the results of the study will help to show the type of case for which this new agent is particularly suitable.

ZUSAMMENFASSUNG

Die Zuverlässigkeit der oralen Cholecystographie wird in 1,340 Fällen, die während der Jahre 1937—1948 im Serafimerlasarettet untersucht worden sind, studiert. Während dieses Zeitraumes sind nur wenige Fälle ohne vorherige Röntgenuntersuchung operiert worden. Nahezu jeder Fall, in dem die cholecystographischen Befunde als

abnorm gedeutet wurden, ist einer Operation unterzogen worden. Das Ergebnis dieser Untersuchung zeigt, dass die Methode ausserordentlich zuverlässig ist. Die Bedeutung schwacher Kontrastfüllung und die Fehlerquellen werden besprochen. Das intravenöse Kontrastmittel Biligrafin war zur Zeit dieser Untersuchungen noch nicht auf dem Markt erschienen. Man hofft, dass die Resultate dieser Studie dazu behilflich sein können, die Fälle zu finden, für welche das neue Kontrastmittel besonders günstig ist.

RÉSUMÉ

Les auteurs étudient sur 1,340 cas du Serafimerlasarettet de 1937 à 1948 la confiance que l'on peut accorder à la cholécystographie orale. Pendant cette période, il n'y a que quelques cas qui ont été opérés sans examen radiologique préalable, et pratiquement tous les cas où la cholécystographie avait été considérée comme anormale ont été opérés. Les résultats de cette étude prouvent que cette méthode est extrêmement sûre. Les auteurs examinent la signification d'une mauvaise imprégnation et les causes d'erreur. Le produit de contraste intraveineux Biligrafin n'était pas encore sur le marché au moment de ces examens. Les auteurs espèrent que les résultats de leur étude contribueront à montrer dans quel type de cas ce nouveau produit est particulièrement indiqué.

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A METHOD OF ANGIOGRAPHY OF THE AZYGOS VEIN AND THE ANTERIOR INTERNAL VENOUS PLEXUS OF THE SPINE

by

Björn Nordenström

With a view to finding a method of treatment for imminent thromboembolism of the lower extremities, ligation of the inferior vena cava has been performed both in laboratory experiments and clinically (5, 7, 1, 8, 15, 17, 12, 13, 9, 16, 10, 11, 14, 4). A relatively large number of patients has been treated by means of ligation of the inferior vena cava, but there is considerable difference of opinion on the value of the method. In some cases, contrast injections have been made in the veins of the extremities in conjunction with experimental ligation or occlusion of the vena cava (13, 11, 14, 4). Contrast filling has then been obtained of the collateral vessels of the inferior vena cava after ligations of long duration.

The present report deals with the possibilities of the roentgenologic examination of the collateral vessels of the inferior vena cava during temporary occlusion of the vein. The primary objective was to investigate the possibilities of angiography of the vessels of the azygos system.

Contrast medium filling of the azygos vein and the internal venous plexus of the spine may be obtained by means of the injection of the medium into a processus spinosus (2, 3). It should also be possible to use the anastomoses existing between the azygos vein and the inferior vena cava for contrast filling of the azygos system. A temporary occlusion of the inferior vena cava should enable a contrast fluid, injected below the occlusion, to be directed through these anastomoses. The effect

This investigation was supported by the James Picker Foundation on recommendation of the Committee on Radiology, National Research Council, Washington.

Submitted for publication, 16 March 1955.

of temporary occlusion of the inferior vena cava at different levels was first studied by measurement of the venous and arterial pressures. Tests were then made to find the most suitable site for occlusion of the vena cava with a view to directing contrast fluid through the anastomoses between the cava and azygos systems.

Material and equipment

The experiments were performed on 13 dogs under intraperitoneal nembutal narcosis. Usually 0.5 ml pentobarbital sodium per kg body-weight was administered (Nembutal, Abbott). The animals were examined in the supine position and, in some cases, lying on one side. A 'balloon catheter, type 4' (6) was used. This consists of a heart catheter with two canals, one of which has a rubber balloon attached to the tip, while the other freely opens proximally to the balloon.

The catheter was introduced via a saphenous or a femoral vein and, under fluoroscopic control, was guided to the inferior vena cava.

The inferior vena cava was occluded by means of the catheter balloon below the renal veins, between the renal and the hepatic veins, or at the opening of the inferior cava into the right auricle. The occlusion of the cava was effected by filling the catheter balloon with iodopyracet 35 % (Umbradil, Astra). Before the balloon was filled, the catheter was fixed against the animal's leg to prevent the blood stream carrying it away in a proximal direction in the vena cava. The sufficiency of the contrast fluid injected into the balloon was controlled by fluoroscopy. When the balloon had become distinctly flattened by the vascular wall it was considered to obstruct the vessel adequately. To prevent coagulation, 1 to 1.5 mg heparin per kg body-weight was injected through the free catheter canal.

Before the injection of contrast medium into the vascular system, the venous pressure was controlled below the occlusion with simultaneous control of the arterial blood pressure. These controls were effected via thick cannulas which were introduced in a femoral vein and a femoral artery. The blood pressure, transmitted through liquid to mercury manometers, was recorded continuously on a kymograph paper.

After occlusion of the inferior vena cava, triiodo-acetyl-amino-benzoate 70 % (Rheopak, Astra) was injected in amounts of 1 ml per kg body-weight through the free catheter canal. The injection time was about 2 to 3 seconds. On conclusion of the injection, 7 to 8 antero-posterior roentgenograms were taken at intervals of about one second between exposures. In a few cases only, the investigation was supplemented with lateral roentgenograms. In these cases, the animals were investigated lying on one side.

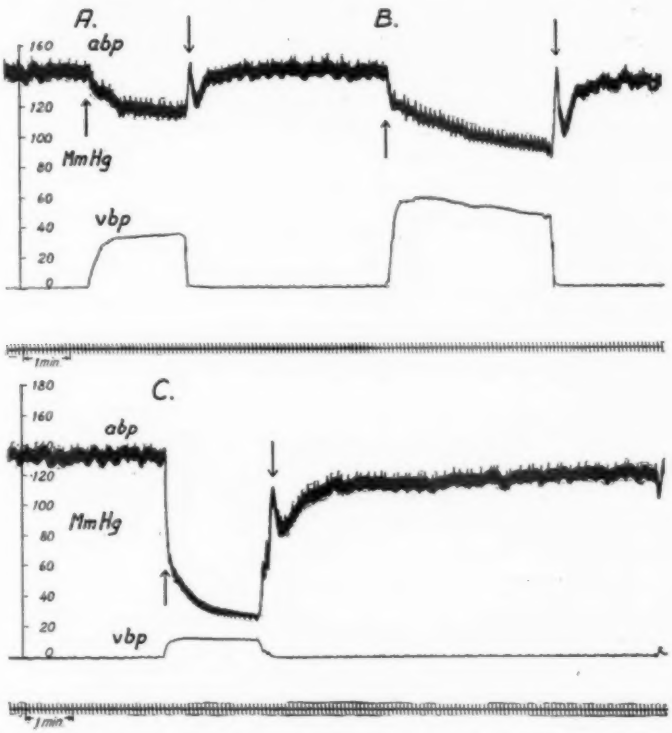


Fig. 1. Pressure changes in the femoral vein (vbp) and the femoral artery (abp) during temporary occlusion (↑) of the inferior vena cava in a 12 kg dog. (↓) = release of the occlusion.

A) Occlusion below the renal veins. B) Occlusion between the renal veins and the hepatic veins. C) Occlusion above the opening of the hepatic veins into the inferior vena cava.

Changes in the venous and arterial pressure on occlusion of the inferior vena cava

Experimental investigations on the changes in the venous pressure in the lower extremities have earlier been made in connection with experimental ligation of the inferior vena cava below the renal veins. The venous pressure then varied within wide limits from the normal 120 mm H_2O up to more than 600 mm H_2O (10) while some investigators (4) appear to have obtained variations of between 100 and 1,250 mm H_2O in the dog. The maximum rise in pressure seems to come immediately after occlusion of the vena cava; it then sinks and reaches its lowest

value after about 15 minutes. It then rises again slowly to a fairly stable value after an occlusion lasting 1 hour (4).

In these experiments, comparisons were made between the arterial and venous pressure with occlusion of the inferior cava at different levels. These occlusions were made: 1) below the renal veins, 2) between the renal and the hepatic veins and 3) above the opening of the hepatic veins into the inferior cava close to the right auricle.

Fig. 1 shows the pressure curves obtained from occlusions of the inferior vena cava in a 16 kg dog. It was found that occlusion below the renal veins (A) gives a moderate reduction of the arterial pressure and a similarly moderate rise of the venous pressure below the occlusion. When the occlusion is removed after a few minutes, both the arterial and venous pressures return fairly rapidly to their original values. If the occlusion of the cava is made between the renal and hepatic veins, similar but more pronounced changes in the pressure are obtained (B). When the inferior cava is occluded above the opening of the hepatic veins, a catastrophic fall in the arterial pressure is obtained, while the venous pressure below the occlusion shows only an insignificant rise (C).

Contrast medium filling of the azygos vein and the anterior internal venous plexus of the spine

For angiography of these two vascular systems temporary occlusions of the inferior vena cava were made, either below the opening of the renal veins or between the openings of the renal and hepatic veins into the vena cava.

Fig. 2a shows an angiogram taken towards the end of the injection of 15 ml Rheopak 70 % in a 15 kg dog in the supine position. The occlusion of the inferior vena cava lay between the hepatic and the renal veins. Besides the contrast-filled inferior cava below the occlusion, the internal venous plexus of the spine may clearly be seen as two longitudinal, fairly large vessels. Somewhat to the right of these and at the level of the liver, an additional third vessel forms the lower part of the azygos vein.

It was found later that the same contrast medium filling may easily be obtained if the occlusion of the inferior vena cava is effected below the renal veins (Fig. 2b). At the same time, filling is often also obtained of the pelvic veins.

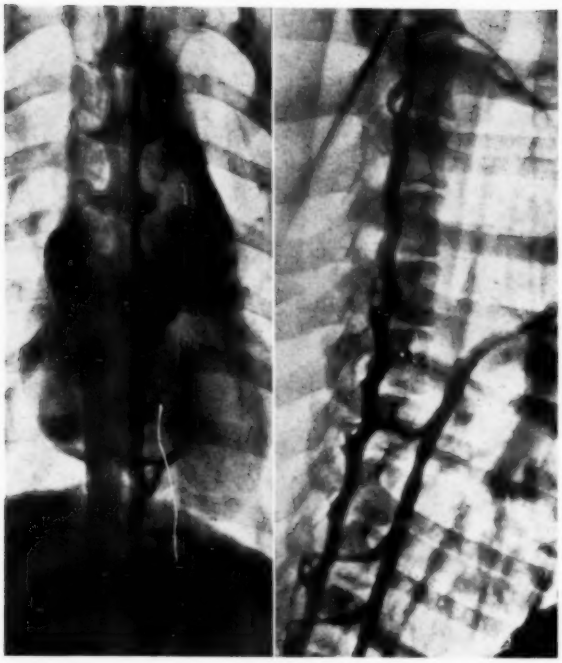
If roentgenograms are taken of the thorax in conjunction with the injections, the contrast-filled azygos vein to its opening into the superior vena cava, as well as the anterior internal venous plexus along the whole of the thoracic spine, may be followed. At the junction between the

a b

Fig. 2. a) A.p. roentgenogram during injection of Rheopak 70 % below an occlusion of the inferior vena cava between the renal and hepatic veins in a dog. Contrast medium filling of the internal venous plexus is produced via anastomoses from the inferior vena cava. Filling of the lower part of the azygos vein can be seen in the upper part of the film. b) In angiography during occlusion of the vena cava below the renal veins, equally good filling of the internal venous plexus of the spine is obtained as in a). Filling of branches of the sacral veins is also obtained.

cervical and thoracic spines the contrast medium passes into the anonymous veins.

Fig. 3a shows an antero-posterior angiogram, and Fig. 3b a lateral angiogram of the upper part of the azygos vein and the anterior internal venous plexus.



a b

Fig. 3. a) A.p. roentgenogram of the thorax of a dog after injection of 1 ml Rheopak 70 % per kg body-weight below a temporary occlusion of the inferior vena cava. Both the azygos vein and the internal venous plexus of the spine are filled. The animal was examined in the supine position. b) Lateral roentgenogram of the same dog. The animal was examined lying on the left side.

Discussion of possible risks

Ligation of the inferior vena cava below the renal veins has been recommended and used by many as a therapeutic measure in thrombosis of the lower extremities. Although the value of such a measure is often considered debatable, it has been shown that it is possible to occlude the inferior cava without causing serious disturbances of the circulation in the lower part of the trunk and the extremities. In these experiments, the occlusion of the inferior vena cava, the injection of the contrast medium, and the release of the occlusion, need not last more than about one minute. The damming up of the blood below the renal veins will hardly be considered as a risk in the investigation. Neither does the application of contrast medium involve any additional risks, apart from those that must always be taken into account with any injection into

the vascular system. The communications between the vena cava below the occlusion and the pelvic veins and veins of the lower extremities, together with the anastomoses of the collateral vessels of the vena cava, appear to afford sufficient protection against serious pressure rises in the vena cava on injection of the contrast medium.

In 12 of the animals, no complications arose. In one provocative experiment, 6 injections were made at about 20 minute intervals. The animal moved freely and was apparently quite unharmed on the days following the investigation. In one experiment the animal was, on the morning of the second day, found to have bled to death. A femoral vein had been used in the catheterisation and the ligature on the vein had presumably slipped or been torn away.

Conclusions

These experiments in dogs indicate that the method introduced for angiography of the azygos vein and the anterior internal venous plexus of the spine may reasonably be considered as suitable for application, in certain cases, in human subjects.

The method has the advantage of being effective and relatively simple. A satisfactory admixture of contrast medium and blood is obtained in the inferior cava. This, together with a probably considerable increase of flow in the azygos vein and the internal plexus of the spine should provide favourable conditions for the study of these vessels.

In experiments in animals, with occlusion of the vena cava below the renal veins, contrast medium filling can be obtained of pelvic veins, the azygos vein, and the anterior internal venous plexus of the spine. The latter vascular system may be outlined from the sacral veins as high as the level of the 7th cervical vertebra.

SUMMARY

A method is described for angiography of the azygos vein and the anterior internal venous plexus of the spine, the inferior vena cava being occluded by means of a special catheter. Contrast medium injected below the occlusion is introduced through the anastomoses from the inferior vena cava to the azygos vein and the anterior internal venous plexus of the spine. Filling of the latter may then be obtained from the sacral veins to the level of the 7th cervical vertebra.

ZUSAMMENFASSUNG

Eine angiographische Methode zur Darstellung der V. azygos und des vorderen inneren Venenplexus der Wirbelsäule wird beschrieben. Hierbei wird die V. cava inferior unterhalb der Nierenvenen mit Hilfe eines Spezialkatheters abgeklemmt. Ein unterhalb des Verschlusses injiziertes Kontrastmittel wird durch Anastomosen von der V. cava

inferior in die V. azygos und den vorderen inneren Venenplexus der Wirbelsäule introduziert. Eine Ausfüllung der letzteren von den sacralen Venen bis hinauf zum 7. Halswirbel kann auf diese Weise erreicht werden.

RÉSUMÉ

Description d'une méthode d'angiographie de la veine azygos et du plexus veineux rachidien antérieur interne, la veine cave inférieure étant obstruée au moyen d'un cathéter spécial. Le produit de contraste injecté au-dessous de l'obstruction passe, par les anastomoses, de la veine cave inférieure à la veine azygos et au plexus veineux antérieur interne du rachis. Ce dernier peut ainsi être injecté des veines sacrées jusqu'au niveau de la 7e vertèbre cervicale.

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MULTIPLE STENOSIS OF THE PULMONARY ARTERIES ASSOCIATED WITH PULMONARY HYPERTENSION, DIAGNOSED BY SELECTIVE ANGIOCARDIOGRAPHY

by

H. Arvidsson, J. Karnell and *T. Möller*

During the years that heart catheterization has been carried out in cardiac and pulmonary diseases, cognition of the pressures in the lesser circulation has increased. Different causes of pulmonary hypertension in man have been mapped out. Fundamental research in this field have been carried out inter alios by COURNAND. LAGERLÖF and WERKÖ et al., have investigated normal pulmonary artery pressure and its variation in cardiovascular disease. From a practical point of view the causes of pulmonary hypertension may be classified as follows:

I. *Increased blood flow through the lungs* (L—R shunts)

Patent ductus arteriosus, septal defects, anomalous venous drainage of the lungs.

II. *Increased resistance in the lungs*

a) Chronic lung diseases: tuberculosis, emphysema, pneumoconioses,

b) Increased resistance in the lung vessels without lung disease, which may be divided into: (1) stasis (left heart failure), *e. g.* mitral disease, (2) increased resistance in the arterioles of the lungs ('primary' pulmonary hypertension), (3) lung embolism with obliteration of the smaller and/or larger pulmonary arteries (chronic lung embolism).

Two cases of pulmonary hypertension of a hitherto unknown cause will be described. Both patients were young individuals in whom the cause of pulmonary hypertension was multiple stenoses of the peripheral lung arteries. The anomalies were in all probability congenital.

Submitted for publication, 13 April 1955.

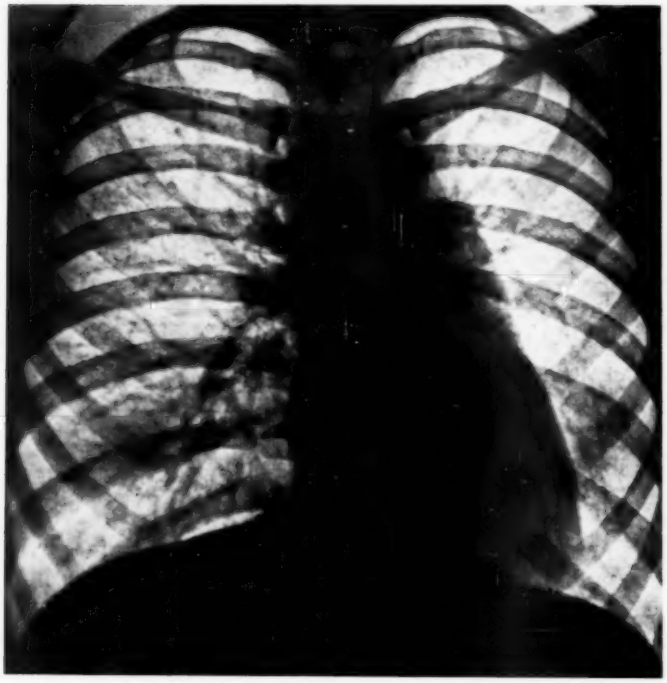

Fig. 1. Case I. Conventional film. No enlargement of the heart but moderate widening of the pulmonary trunk. The central lung vessels are a little wider than normal.

Case Reports

Case I. A. J., a girl, aged 13, physically and mentally underdeveloped since early childhood, had with some difficulty attended school. Impaired vision was noted at the age of eleven and a physician was consulted. A general clinical examination was considered necessary since heart disease was suspected. She was referred to the Pediatric Clinic at the age of thirteen.

Physical examination: Physical and mental development, roughly corresponding to a child of 9 years. Weight 27 kg, height 134 cm. *Heart:* No failure, cyanosis, or clubbing; no deformity of the chest. There was no precordial thrill and the rhythm was normal. A continuous murmur, beginning in systole and continuing throughout diastole was heard over the entire chest. The pulmonary second sound was accentuated. B. P.: (arms) 115/70, (legs) 160/90. Blood: R. B. C. 4 mill. Hgb 76 %, W. R. negative. ECG showed right axis deviation and high peaked P-waves but otherwise no pathologic changes.

Roentgen examination of the heart and lungs (Fig. 1): Heart normal in size, volume 290 cc, corresponding to 280 cc per sq. meter body surface. The pulmonary trunk as well as the main branches were wide. The vascularization of the peripheral parts of the lungs was normal.

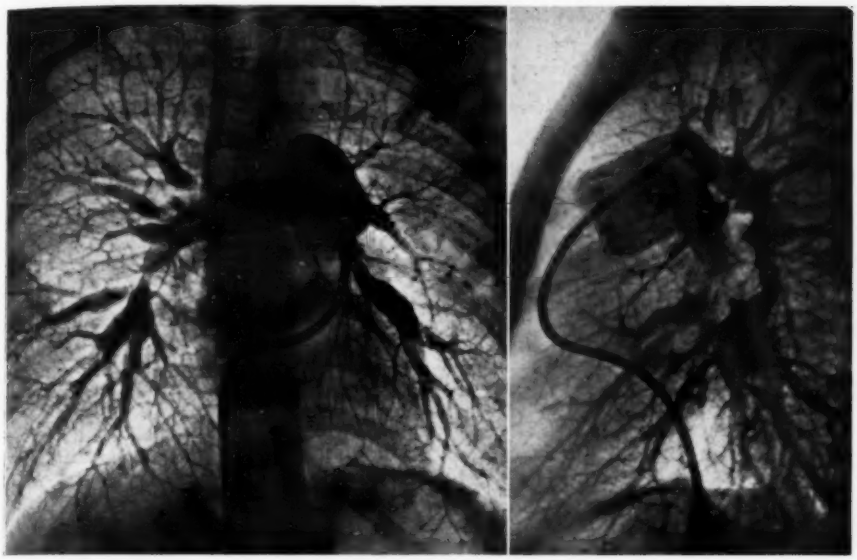

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Fig. 2. Case I. Angiocardiography. a. A. p. view. Arterial phase of the lung circulation. The tip of the catheter is in the pulmonary trunk. The multiple stenoses as well as the post-stenotic dilatations of the pulmonary arteries are clearly visible. b. Lateral view, exposed simultaneously with a.

In view of the presence of a continuous murmur, a preliminary diagnosis of patent ductus was made. Heart catheterization was performed through the right superior vena cava. There were no signs of a L—R shunt. The pressure in the pulmonary artery was abnormally high, P. A. pressure 56/18 mm Hg and R. V. 60/7. The oxygen saturation in the brachial artery was 98 %. Angiocardiography with injection in the sup. vena cava showed normal shape and size of the right side of the heart. The pulmonary trunk and the main branches were dilated, but the peripheral branches narrow. It was not possible to discern the lung vessels or the left side of the heart in detail because of the imperfection of the method of injection.

The examination had not verified the diagnosis of patent ductus. However, because of the continuous murmur and pulmonary hypertension it was decided to carry out thoracic aortography; this was performed at Södersjukhuset. The aorta including the valves were normal and no shunt was found. After this examination, so-called primary pulmonary hypertension was substituted as the tentative diagnosis.

The patient returned to the Pediatric clinic two years later for a follow-up examination with the same symptoms as previously.

Physical examination: Early puberty; weight 34 kg, height 141 cm. *Heart:* Auscultatory findings as previously. B. P. (arm) 135/80. Roentgen examination of the chest showed increased volume of the heart, 480 cc corresponding to 410 cc per sq. meter body surface, otherwise the picture was unchanged. A more thorough examination of the pulmonary artery was now indicated.

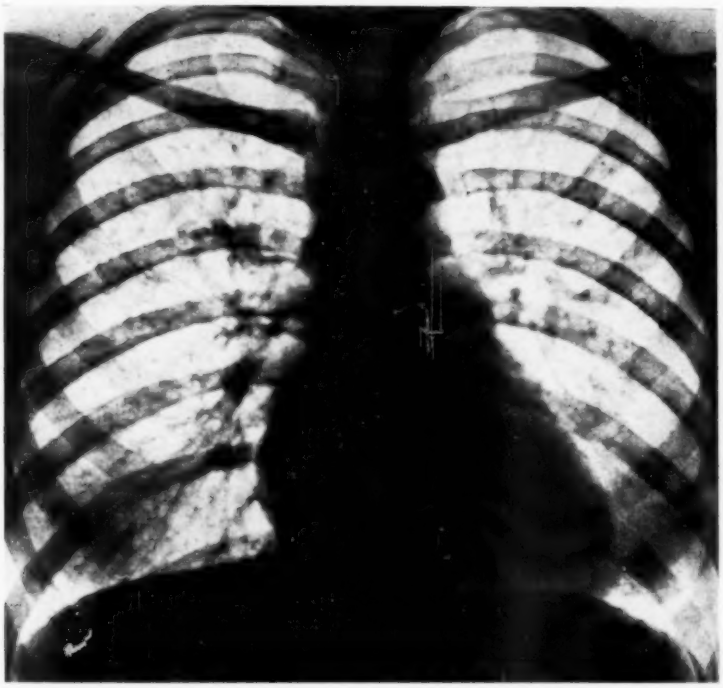

Fig. 3. Case II. Conventional film. Moderate enlargement of the heart and slight dilatation of the pulmonary trunk. The vascularization of the upper part of the lung is slightly irregular.

Catheterization and angiocardiography: A second heart catheterization showed a marked increase in the P. A. pressure, 78/31 mm Hg, mean 44 mm and R. V. 78/0. Blood gas analyses were identical with those of the previous examination. A catheter No. F 10 was introduced through a saphenous vein, so that its tip reached the pulmonary trunk. Fifty (50) ml iodopyracet (Umbradil) 70 % were injected by means of a pressure apparatus. Ten (10) pairs of films were exposed during 6 seconds (Fig. 2 a and b).

The pulmonary trunk was dilated (diameter 4 cm). There were marked short narrowings of the lumina of all the lobar arteries. The diameter of the vessels in the stenosed areas was only 2 to 3 mm and, in places, the lumina were as fine as threads. The diameter of the vessels on the heart side of the narrowings was 8 to 10 mm. Spindle-shaped poststenotic dilatations with a diameter up to 12 mm were noted peripherally and, distal to these, the vessels were narrow. In spite of the malformation, the contrast medium was apparently circulating through the lungs at approximately normal velocity and rendering the left side of the heart and the aorta opaque 5 seconds after the injection.

Case II. U. A., female, aged 19, of normal development until the age of ten, when she became short of breath more easily than her class-mates. Her condition remained unchanged until the age of 18 when she was admitted for the first time.

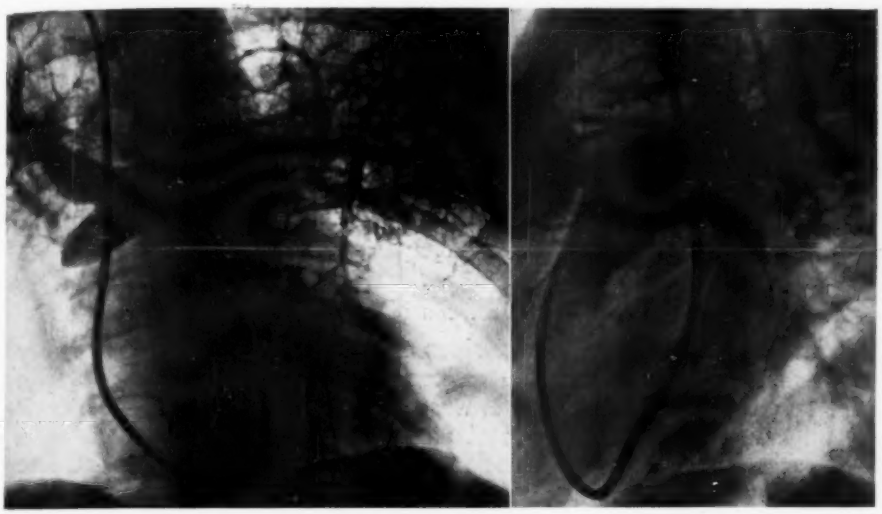

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Fig. 4. Case II. Angiocardiography. a. A. p. view. Arterial phase of the lung circulation. The tip of the catheter is in the pulmonary trunk. A small amount of contrast medium lies in the pulmonary conus due to recoil of the catheter. There are no pulmonary arteries in the lower parts of the lungs. Note the anomalous arborisation of the arteries in the upper parts of the lungs. b. Lateral view. Exposed simultaneously with a.

Physical examination: Slender girl in apparently good health; weight 63.5 kg, height 172 cm. No dyspnoea at rest, clubbing or chest deformity. *Heart:* A high-pitched systolic murmur was heard at the apex. At the base of the heart there was a long, harsh systolic murmur which also could be heard over the carotid arteries. Pulsus celer. B. P. (arm) 150/60. *Blood:* R. B. C. 4.3 mill. Hgb 84 %. W. R. negative.

Roentgen examination of the heart and lungs (Fig. 3): The volume was 900 cc corresponding to 510 cc per sq. meter body surface. The heart was moderately enlarged with preponderance of the right ventricle. There was some widening of the pulmonary trunk. The central lung vessels were wide and very irregular. The peripheral vessels were of normal size. No abnormal pulsations were seen during fluoroscopy.

Catheterization and angiocardiography: No abnormal passage could be found between the right and left sides of the heart on venous catheterization. The blood gas analyses showed no L—R shunt. The pressure measurements revealed increased pressure both in the right ventricle and the pulmonary artery. P. A. pressure 56/13 mm Hg, mean 32 mm; the pressure in the brachial artery was 143/83 mm, mean 98 mm.

A catheter No. F 10 was inserted through a cubital vein on the right side, so that the tip at the time of the injection lay in the pulmonary trunk. Seventy-five (75) ml iodopyracet 70 % were injected during 3.5 seconds. Ten (10) pairs of films were exposed over 6 secs, simultaneously in frontal and lateral projections (Fig. 4 a and b). During the injection the catheter recoiled to the infundibulum for a short time. The pulmonary conus, the valves, and the pulmonary trunk, presented a normal appearance. The right main branch of the pulmonary artery was a little wider than normal. Only the upper

parts of the lungs received vessels from the pulmonary artery. No contrast filling of the lower portions, approximately corresponding to both lower lobes, the right middle lobe, and the (left) lingular lobe, was obtained. The right pulmonary artery divided into one upper and one lower branch, the latter terminating in a blind pouch approximately 3 cm from the bifurcation of the right pulmonary artery. The upper branch of the right pulmonary artery was wide and divided abruptly into several wide, irregular arteries, one of which was stenosed with a marked post-stenotic dilatation. The left lower lobe received no branches from the pulmonary artery. The artery to the upper part of the left lung was of normal width. The arborization of the pulmonary artery was of the type which is known to occur in pulmonary hypertension. The circulation through the lungs was relatively rapid, the left atrium becoming opaque some 3 secs after the beginning of the injection.

Discussion

In these two cases it is obvious that the cause of the pulmonary hypertension was the resistance exerted by the multiple stenoses upon the lesser circulation. In Case I, there was an increased resistance in all the branches, without any total stenoses. The post-stenotic dilatation that was found at every stenosis had the same genesis as post-stenotic dilatations in other situations, viz. the hydrodynamic forces acting on the walls of the vessels (HOLMAN).

In Case II, the pulmonary vascular bed was reduced, mainly due to the total obliteration or aplasia of the lower lobe arteries. The inferior portions of the lungs received their blood supply from the bronchial arteries, which became opaque at the same time as the aorta. They were moderately widened. No anomalous vessel from the greater circulation could be observed.

Multiple stenoses of the pulmonary arteries as a cause of pulmonary hypertension has, as far as we know, not previously been reported in the literature. SØNDERGAARD has described three cases of what he calls coarctation of the pulmonary artery, in which there were stenoses in the pulmonary trunk but not in the peripheral vessels.

The diagnostic difficulties are obvious from the case histories. The absence of pathology reports of similar cases should indicate that the two cases described are great rarities and without clinical interest. The situation of the stenoses, however, is such that they are easily missed by routine autopsy. Furthermore, pulmonary hypertension is seldom considered as an indication for angiocardiography and even if this is performed, the anomalies may be overlooked (cf. Case I). The selective method of injection gives a precise anatomic picture of the arteries of the lungs and reveals small anomalies of the vessels.

Addendum

Since this report was written we have seen two cases with almost the same appearances as the ones described. These will be only briefly

Fig. 5. Case III. Angiocardiography. A. p. view. Arterial phase of the lung circulation. The tip of the catheter is in the pulmonary trunk. Hypoplastic pulmonary artery. The stenoses of the branches are not so well seen as in Cases I and II. Moderate post-stenotic dilatations are visible, especially in the lower part of the right lung and the upper part of the left. Varnauskas' double balloon catheter blocking the atrial septal defect.

discussed. The two patients were mother and son with a family history of heart disease.

Case III (from Garnisonssjukhuset (Director: Docent H. LAGERLÖF), Stockholm). S. W., female aged 33, with a history of heart disease since early childhood. Admitted for precordial pain and tachycardia. *Heart:* Systolic murmur, Grade III, heard over the entire heart as well as over the back. B. P. (arm R = L) 165/55 mm Hg, (leg) 230 mm Hg systolic.

Catheterization and blood gas analyses showed an atrial septal defect with L—R shunt and pulmonary hypertension (Pressure P. A. 72/7 mm Hg, mean 27 mm).

Angiocardiography was performed with a Varnauskas double balloon catheter blocking the septal defect. The injection of contrast medium was carried out with another catheter, the tip of which was placed in the pulmonary trunk (Fig. 5). Fifty-five (55) ml Rheopak (Astra) 70 % were injected during two secs. The trunk of the pulmonary artery as well as the main branches were hypoplastic. Multiple stenoses with post-stenotic dilatations were present in the secondary branches. The stenoses were not so well seen as in Cases I and II, but the post-stenotic dilatations were clearly visible. In spite of the

stenoses, the circulation through the lungs was relatively rapid. No vessels were seen entering the right atrium during the venous phase.

The diagnosis was multiple stenoses of the peripheral pulmonary arteries and an atrial septal defect complicated with pulmonary hypertension.

Case IV (from Dr. Å. LUNDBERG and to be reported elsewhere). I. W., a boy, aged 10, with heart trouble since early childhood; cyanotic on exercise. On auscultation: a coarse systolic murmur with point of maximum intensity in the left second interspace. B. P. 110/65.

Catheterization: There was no sign of a shunt. Pressure in the pulmonary trunk: 108/22 mm.

Angiocardiography: The main trunks of the pulmonary arteries to both lungs were hypoplastic, and in addition there were some intrapulmonary stenoses of the lobar arteries with moderate post-stenotic dilatations.

SUMMARY

Four cases of pulmonary hypertension are described. A malformation of the pulmonary artery and/or its branches was present in all the cases and was diagnosed by selective angiocardiography.

ZUSAMMENFASSUNG

Vier Fälle mit pulmonaler Hypertension werden beschrieben. Eine Missbildung der A. pulmonalis und/oder ihrer Verzweigungen lag in sämtlichen Fällen vor und wurde mit Hilfe der selektiven Angiocardiographie diagnostiziert.

RÉSUMÉ

Les auteurs présentent quatre cas d'hypertension pulmonaire. Il existait dans tous les cas une malformation de l'artère pulmonaire et/ou de ses branches, qui fut diagnostiquée par l'angiocardiographie sélective.

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FROM THE INSTITUTE OF RADIOLOGY (DIRECTOR: PROF. ARDUINO RATTI), UNIVERSITY OF PAVIA, ITALY, AND ROENTGEN DEPARTMENT I (DIRECTOR: DOCENT G. JÖNSSON), SÖDERSJUKHUSET, STOCKHOLM, SWEDEN

THE SIGNIFICANCE OF THE LATERAL SUBSEGMENTS OF THE LUNG IN PULMONARY DISEASE

A Review of 500 Cases

by

L. Di Guglielmo and *B. Bonomo*

Many authors in studying the segmental structure of the lung have recognized the existence of lateral or axillary regions and point out that certain bronchi and arteries run a true lateral course from the hilum to the lateral or axillary parts of the lung.

As the axillary bronchi, however, very often do not have an independent origin but start from other segmental bronchi and, in addition, show wide variations, the latest classifications include the axillary regions as subsegments of more constant segments or deny their separate existence altogether. There can be no doubt, however, that these regions have a particular significance in pulmonary disease. In fact, all authors who have studied segmental lesions of the lung radiologically, agree that these regions may frequently be the seat of various intrinsic morbid processes.

The scope of the present study is to establish, in a large number of cases, the frequency with which the lateral subsegments of the lung are involved in morbid processes affecting individual lobes, and whether the radiologic appearances of these lesions are constant and what constitute their characteristic features.

Material

The study covers 500 cases of various segmental pulmonary lesions seen during the last 4 years, consisting of 253 cases from the Institute,

Submitted for publication, 3 September 1954.

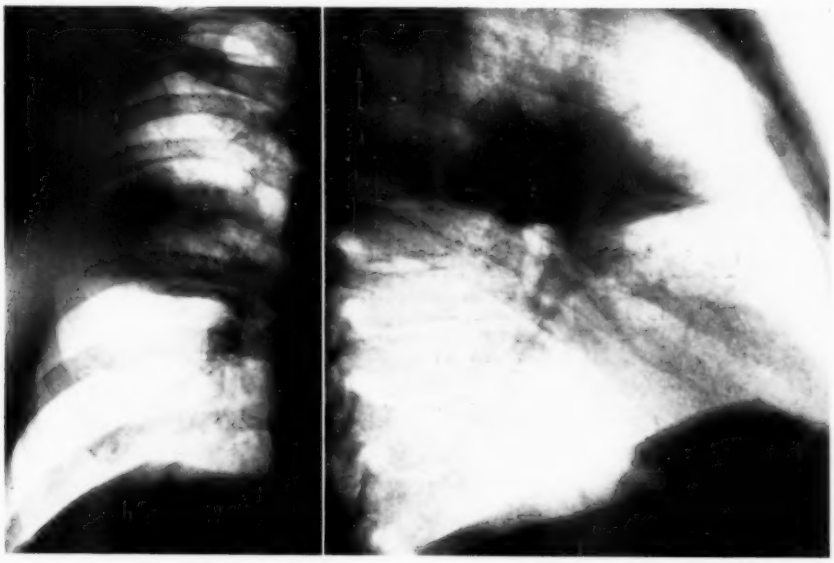

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Fig. 1. Consolidation of the lateral subsegment of the right upper lobe. a) P.a. Band-shape density with clear-cut lower margin corresponding to the horizontal fissure. b) Lateral The opacity has a median situation and rides the point where the two fissures meet.

and 247 cases from the Roentgen Department I of Södersjukhuset, Stockholm. Only cases in which the lesion was strictly confined to one or more segments have been included. In a large number of these cases, the diagnosis and localization of the lesion were confirmed both bronchographically and bronchoscopically.

Findings. Out of the 500 cases, 459 patients had lesions involving only one segment while 41 had changes affecting two or more segments of the same or different lobes, or of the other lung. The following data were obtained.

A lateral situation was found in 23 % of our cases in various diseases showing that the incidence is high. These lesions showed the same features in the right as in the left lung.

A lateral situation was found in the upper lobe in 11.1 %, in the middle lobe in 4.9 %, and in the lower lobe in 7.1 % of cases. In the latter lobe, a lateral situation rarely occurs in the apical region (1.09 %), while it is much more frequent at the base (6.1 %), particularly of the left lung. The axillary region was completely involved in 46 cases

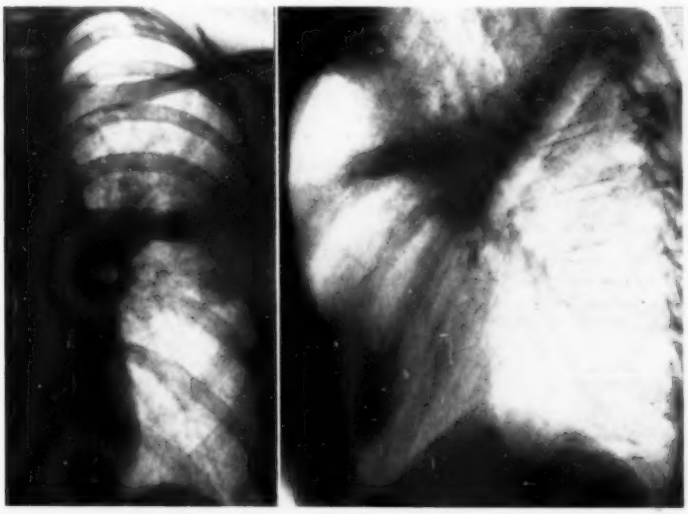

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Fig. 2. Consolidation of the lateral subsegment of the left upper lobe. a) P.a. The triangular opacity is laterally situated. b) Lateral. The density lies above the hilum. Close analogy with the consolidation of the same right subsegment although by reason of the absence of a horizontal fissure the lower border is not sharp anteriorly.

of upper lobe disease, while only in 3 cases was the anterior part and in 4 cases only the posterior part affected.

Radiologic opacity of the axillary regions is constant in the various diseases and has clear-cut characteristics for each individual lobe. All axillary subsegments generally appear in the p.a. projection as more or less triangular opacities with the apices pointing towards the hilum and the bases in contact with the lateral thoracic wall. They are distinctly external and always well separated superiorily from the pulmonary apex and inferiorily from the diaphragm. They have no connection whatsoever with the mediastinum. In the lateral projection, the opacity of these regions appears triangular or quadrangular, is clearly outlined, very dense, and easily distinguishable from the pulmonary apex, the anterior and posterior thoracic walls, and the diaphragm. It is always centrally situated and together with the lateral subsegments forms a shadow around the hilum.

Discussion

In 1949, an international commission met in London in order to bring uniformity into the terminology and classification of the division

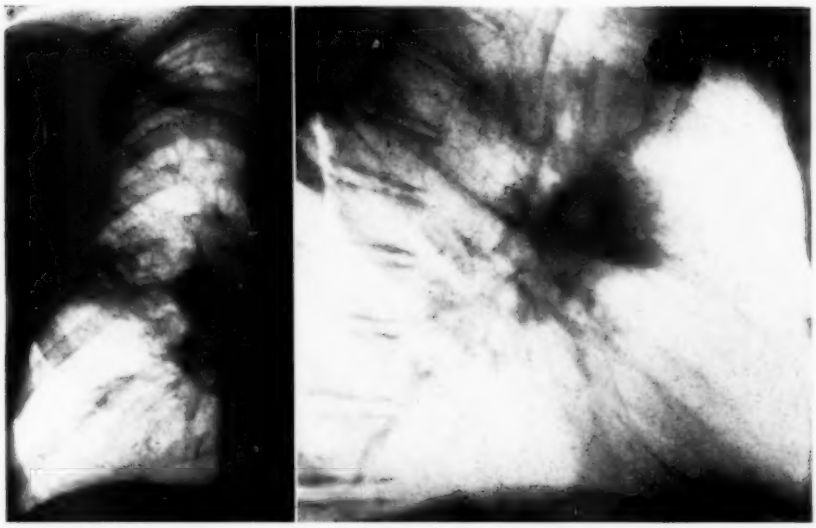

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Fig. 3. Consolidation of the lateral subsegment of the right upper lobe. a) P.a. b) Lateral. The density is situated anteriorly above the horizontal fissure and corresponds to the lateral branch of the anterior segment.

of the lung. Owing to its simplicity the terminology suggested by the commission has been widely adopted. Many who have subsequently studied the problem have been inclined, however, to criticize the classification; many radiologic, bronchographic, and endoscopic findings, undoubtedly cannot be covered by it. The lateral, axillary, or external, regions have particularly been discussed in this connection. (KRAMER and GLASS; NEIL, GILMOUR and GWINNE; COULOUMA; WAREMBOURG and GRAUX; SCHAEPELYNCK; DI GUGLIELMO and GAUDIERI; SOULAS and MOUNIER-KUHN; CONCINA and MINETTO; STUTZ and VIETEN.)

In the p.a. roentgenogram, an opacity in the lateral subsegment of the upper lobe is almost always situated below the clavicle; it is triangular in shape and its clear-cut lower margin corresponds to the horizontal fissure (Fig. 1 a). In the lateral projection the opacity has a characteristic appearance. Its lower border is formed posteriorly by the upper part of the oblique fissure and anteriorly by the horizontal fissure; it thus rides on the point where the two fissures meet (Fig. 1 b). Its appearance on the left side is often the same though no horizontal fissure exists (Fig. 2). Fig. 3 shows a case in which the opacity was situated entirely above the horizontal fissure, corresponding only to the anterior

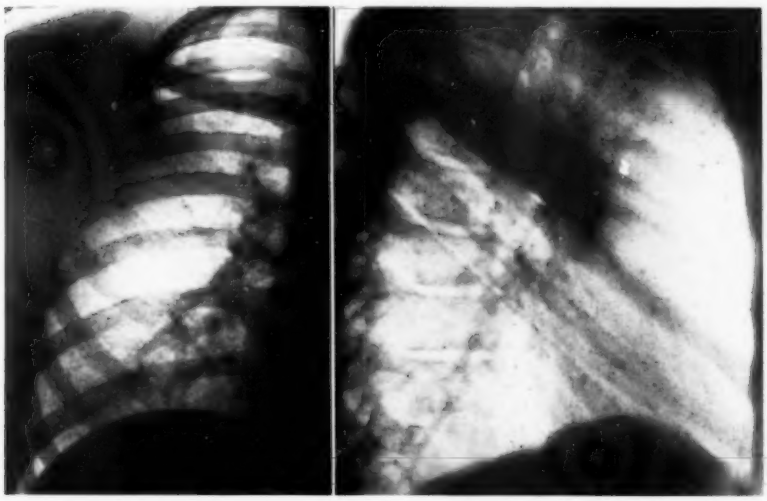

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Fig. 4. Consolidation of the lateral subsegment of the right upper lobe. a) P.a. b) Lateral. The opacity is in contact only with the oblique fissure and does not reach the horizontal fissure anteriorly. It corresponds to the lateral branch of the posterior segment.

part of the territory so far described. Fig. 4, on the other hand shows an opacity situated entirely at the oblique fissure corresponding only to the posterior part of the same region. Such changes are rare on the right; we have never found them on the left.

As regards the upper lobe the concept most widely accepted today is the one formulated by BROCK, according to which each segmental branch (apical, anterior, and posterior) furnishes a lateral or axillary branch destined to supply a corresponding axillary 'area'. This is not in accordance with our observation that in the great majority of cases the axillary region of the upper lobe is wholly involved in the morbid process. It is, in fact, difficult to understand how two or more 'areas' of different segments can be simultaneously diseased while the remaining parts of the segments to which they belong are left undamaged. Moreover, BROCK's concept is not in agreement with the extreme rarity with which single 'areas' are involved.

Almost all students of the segmental structure of the lung concede the possibility, be it a rare one, that in the upper lobe a lateral bronchus originates directly from the lobar bronchus and thus assumes the characteristics of a segmental bronchus, spreading in a well-defined lateral segment. This has been seen in the right lung by D'HOUR et coll. in 10 %,

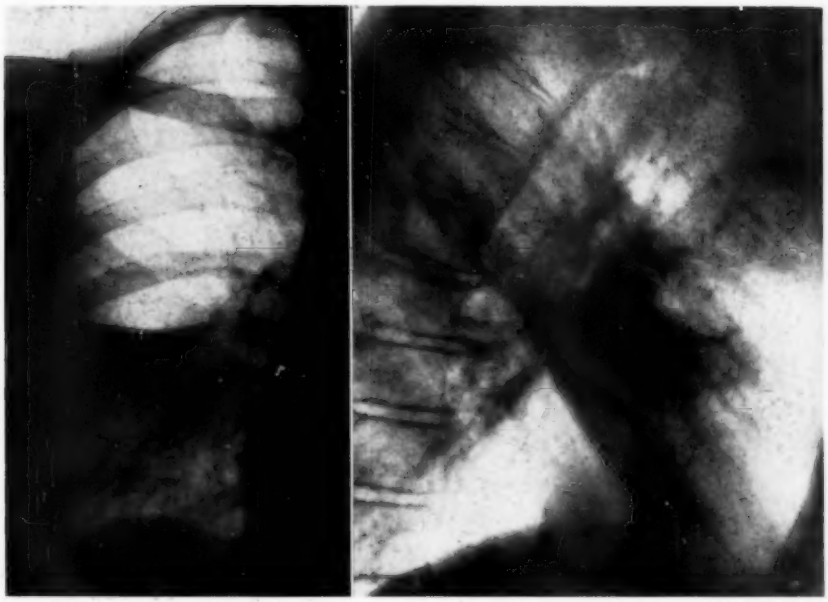

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Fig. 5. Consolidation of the lateral segment of the middle lobe. a) P.a. b) Lateral.

by MINET in 18 %, by SCHAEPELYNCK in 14 %, by ARNAUD et coll. in 14 %, and by CONCINA and MINETTO in 10 % of cases. BOYDEN and SCANNEL dissected 50 lungs and in 16 % found this bronchus with an independent origin, though they never found the same phenomenon in the anterior bronchus. VAGO studied the endoscopic appearance of the segmental bronchi of the right and the left upper lobe in 100 patients. In 11 cases, he found a quadrifurcation at the independent origin of the lateral bronchus.

In the course of a bronchographic examination it is often possible to find an autonomous origin of a large axillary bronchus. HOHN and VIETEN, and later STUTZ and VIETEN, have observed the independence of a definite axillary segmental bronchus in from a fifth to a third of the cases studied bronchographically.

It may, therefore, be taken for granted that a fourth autonomous segmental bronchus, the lateral bronchus ventilating a clearly defined lateral segment, exists in the upper lobe, with an incidence of from 10 % to 18 %.

Supernumerary incisurae on the outer surface of the lung may indicate

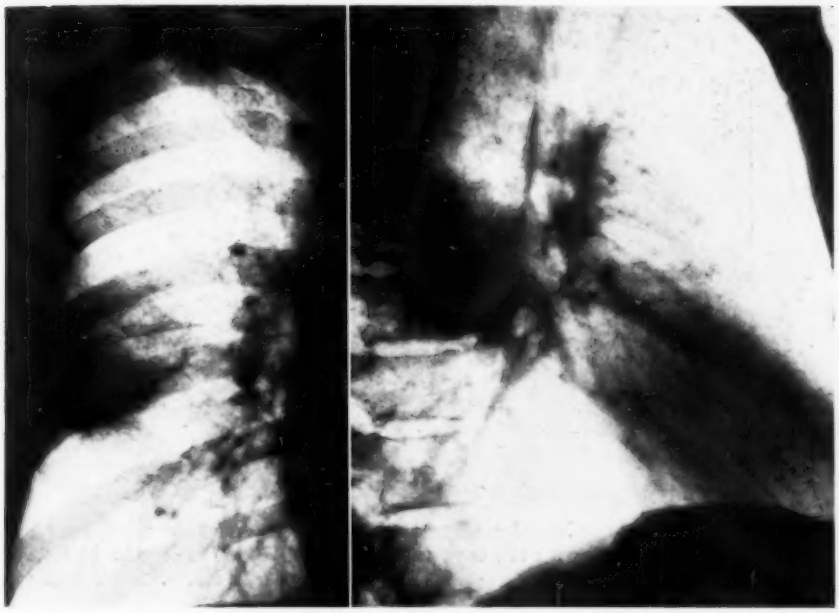

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Fig. 6. Consolidation of the lateral subsegment of the apical part of the right lower lobe. a) P.a. Irregular opacity laterally situated and independent from the horizontal fissure. b) Lateral. The opacity is triangular and situated behind the hilum. It is directed superiorly from the horizontal fissure and separated from the thoracic wall posteriorly.

this lateral segment. While a complete supernumerary fissure is rare (WAREMBOURG and GRAUX), partial fissures between the lateral and the posterior or anterior regions have been observed more frequently.

BOYDEN and SCANNEL's studies have yielded another very interesting fact, namely, that in cases in which there is no lateral bronchus of independent origin, 26 % have the posterior axillary branch displaced in such a way that its axis lies over the crossing of the fissures, thus also aerating the area situated above the horizontal fissures. In 18 % of the cases the same applies to the lateral ramification of the anterior branch which thus also aerates the surface above the oblique fissure.

BROCK, too, speaks of the possibility that one of the axillary branches, originating from the anterior or the posterior bronchus may be specially developed "supplying the greater part of the axillary area by itself" (Fig. 10).

SCHAEPELYNCK has observed that, independent of its autonomous origin, the axillary bronchus of the upper lobe, be it on the right or

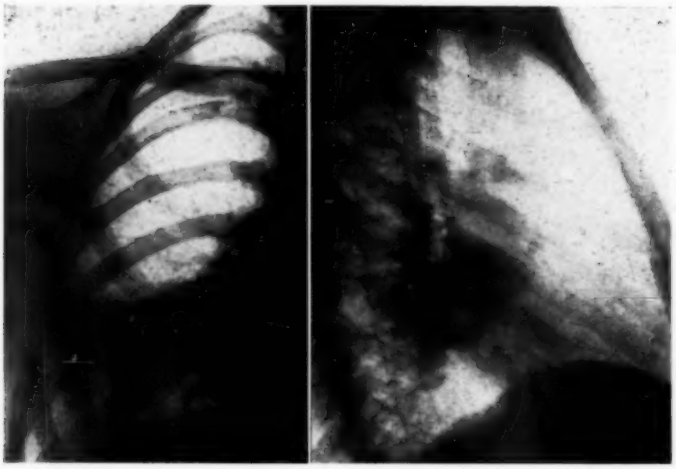

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Fig. 7. Consolidation of the lateral subsegment of the basal part of the right lower lobe. a) P.a. Triangular opacity with the base in contact with the thoracic wall. b) Lateral. The opacity is very dense, well delimited, and lies below the hilum. The apical part of the lower lobe is not affected.

left side, is single in roughly 70 % of cases. WAREMBOURG, GRAUX and PRÉVOST found two upper axillary branches in only 4 out of 14 left lungs. In the London International Classification, the left lung is shown as having only one lateral branch originating from the anterior bronchus. This would explain why in pathologic conditions the consolidation in the vast majority of cases involves the whole lateral region astride the crossing of the fissures and the extreme rarity of circumscribed lesions in the anterior or posterior part only, according to BROCK's concept. One may thus conclude that, apart from those cases (about 15 %) in which there is an autonomous lateral bronchus and an autonomous lateral segment, in the great majority of cases, one of the two lateral branches originating from the posterior, or less frequently from the anterior bronchus, is particularly developed and runs with its axis astride the crossing of the fissures; furthermore, it supplies a well-defined area very similar to the lateral segment described in those cases in which there is an autonomous lateral bronchus. On the other hand, the cases in which there are two equally developed lateral branches and two true lateral subsegments (an anterior and a posterior) are in a minority. This might explain why many authors believe in the existence of only one lateral segment or subsegment in the upper lobe.

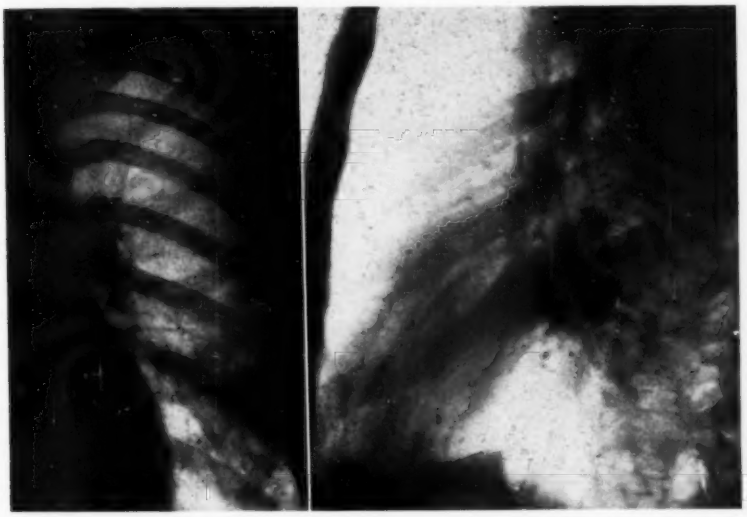

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Fig. 8. Consolidation of the lateral subsegment of the basal part of the left lower lobe. a) P.a. Triangular opacity situated laterally. b) Lateral. The opacity lies below the hilum and is delimited anteriorly from the oblique fissure. Deformity of the diaphragm by pleural adhesions.

The simultaneous involvement of two or more axillary 'areas' depending on different subsegmental bronchi, has never been satisfactorily proved. The radiologic appearances we have described may be more easily explained in a small number of cases as infiltration in a true autonomous lateral segment and in the majority of cases as infiltration in a more developed lateral subsegment which lies astride the crossing of the fissures. In these cases the remaining axillary areas are small and without real significance.

The existence of an autonomous lateral bronchus in the middle lobe has been acknowledged by all authors. As in the majority of cases the middle lobar bronchus divides into an anterior and a lateral branch, the latter is described as a segmental bronchus, even in the London International Classification. It should, however, be remembered that the anterior branch divides into two important ramifications. In a fair number of cases the lateral bronchus does not originate directly from the middle lobar bronchus but from one of these two ramifications.

On the left side the lingular bronchus usually divides into an upper and a lower branch, while the lateral branch originates as a subsegmental ramification from either. This explains the lesser frequency with which

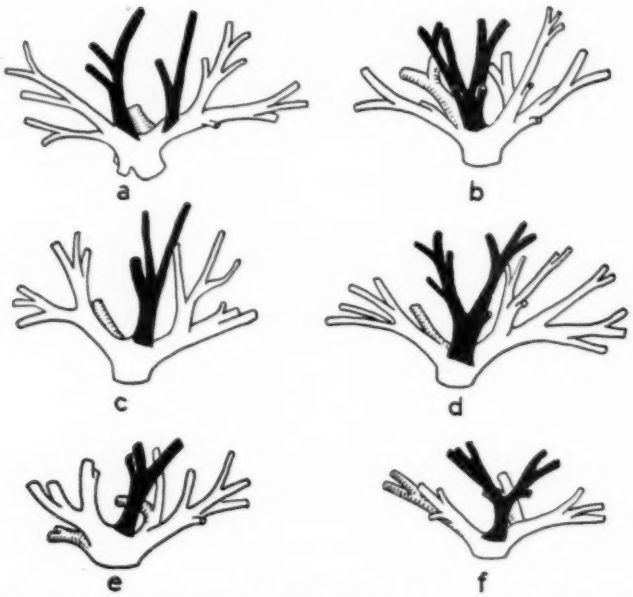
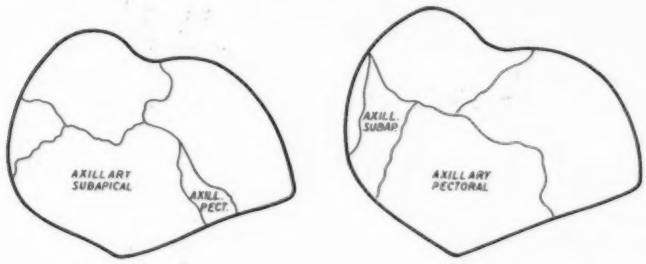


Fig. 9. Six bronchial trees viewed from fissural side of the right upper lobe (from SCANNELL and BOYDEN, modified). The lateral branches are black and the apical branches shaded. a) Two lateral branches arise from the anterior and the posterior branches, respectively — the most common condition. b, c, d, e, f) A lateral branch arises directly from the upper lobe bronchus.

infiltrations analogous to those of the right lateral segment are seen. In about 30 % of cases, however, the lingular bronchus may also divide into an anterior and a lateral branch. VAGO has shown endoscopically that the autonomous origin of the lateral branch of the lingula is quite common.

Consolidation of the lateral segment of the middle lobe has a very characteristic appearance in a lateral roentgenogram. The opacity is triangular with the apex pointing towards the hilum and the base directed forwards, though it is clearly separated from the anterior thoracic wall. Its upper and lower borders are well defined, being formed by the horizontal and the oblique fissures respectively (Fig. 5 b). In a p.a. projection the opacity appears as a triangle in the middle third of the thorax and is frankly external (Fig. 5 a).

On the left side, lesions of the lateral subsegment of the lingula are much less frequent, but opacities identical with those described on the right may be found. In the absence of the horizontal fissure, the upper margin obviously cannot be so clearly defined.



a b

Fig. 10. Inequality of development of the axillary areas in the upper lobe (according to Brock). a) The lateral branch arising from the posterior segmental bronchus aerates almost the whole axillary area. b) In these cases the lateral branch of the anterior segmental bronchus is markedly developed and supplies almost the whole axillary area.

In most cases morbid processes involve the whole of the apical part of the lower lobe. The possibility of a circumscribed lesion in its lateral subsegment has been discussed by Warembourg and Graux, Di Guglielmo, and Concina and Minetto. Schmid has recently called attention to the circumscribed lesion of the area supplied by the lateral branch of the apical bronchus of the lower lobe. Fig. 6 shows one illustrative case of consolidation of this subsegment. While this situation is undoubtedly rare, the fact that in the lateral projection the posterior margin of the opacity is covered by the vertebral column probably accounts for many circumscribed lesions of the lateral subsegment being classified as consolidation of the whole apex of the lower lobe. The circumscribed lesion of the lateral subsegment should, therefore, be regarded as less rare than it appears to be. By largely eliminating the dense shadow of the vertebral column, tomography should be very useful for more exact localization.

The autonomy of one or more axillary subsegment in the base of the lower lobe has been postulated by Coulouma, Warembourg et coll., Di Guglielmo and Gaudieri, Lambertini and Catalano, and recently by Grasso, and Concina and Minetto. The Anglo-American literature, however, has never described these subsegments in detail. On the other hand, Boyden and Scannel have described the bronchial, arterial and venous branching that supplies these regions, and in Boyden's latest publication there is a case in which the lateral branches are particularly well developed.

Brock concedes the possibility that an axillary bronchus may sometimes originate directly from the lower lobe bronchus. Our observations show that the lateral region of the base of the lower lobe of the right as well as the left side is quite frequently (6.33 %) the seat of various

morbid processes and that such lesions have well defined radiologic features which generally render exact localization possible.

In the p.a. projection, the opacity appears as a bundle or triangle situated in the lower third of the lung extending from the hilum to the lateral thoracic wall. It is separated from the diaphragm by normally translucent parenchyma (Figs. 7 a and 8 a). In the lateral projection the opacity has regular margins, is very dense, lies below the hilum, and is frankly median. Its anterior superior margin is formed by the oblique fissure, while the posterior superior margin lies just below the apical part (Figs. 7 b and 8 b). Appearances identical with those described may be found in the publications of other authors even though the interpretations may be different.

Conclusions

The lateral regions of the lungs, even if classified as subsegments, are of considerable importance, being often the seats of a large number of morbid processes. Their bronchi and blood vessels are subject to many anatomic variations but they have certain basic features which are sufficiently constant to be distinguished and classified within an unambiguous scheme.

The radiologic characteristics of the consolidation of these regions are clear-cut and constant. The recognition of the existence of these areas will consequently provide the means for precise localization.

SUMMARY

Based upon a study of 500 cases of various segmental pulmonary changes, the authors discuss the frequency with which the lateral segments are involved and describe the characteristic and constant features. The literature on the segmental structure of the lung is surveyed and, from the authors' own observations, certain modifications of concepts suggested.

ZUSAMMENFASSUNG

Auf Grund eines Studiums von 500 Fällen mit verschiedenartigen segmentalen Lungenveränderungen diskutieren die Verfasser die Häufigkeit von Veränderungen in den lateralen Segmenten und beschreiben die charakteristischen und konstanten Befunde. Die Literatur über die segmentale Struktur der Lunge wird überblickt, und auf Grund eigener Beobachtungen werden gewisse Modifikationen der Begriffe vorgeschlagen.

RÉSUMÉ

Se basant sur une étude de 500 cas de diverses affections pulmonaires segmentaires, les auteurs discutent la fréquence de l'atteinte des segments externes et en décrivent

les traits caractéristiques et constants. Ils passent en revue la littérature sur la structure segmentaire du poumon et, d'après leurs propres observations, suggèrent quelques modifications de conception.

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SIMULTANEOUS STEREOANGIOGRAPHY

by

I. Fernström and *K. Lindblom*

The wealth of vascular detail produced in angiography makes the combination of stereoscopy particularly instructive and valuable. This method was used earlier (HÄUSSLER 1938; ZIEDSES DES PLANTES 1950, and others) but has never really been accepted as the one of choice, necessitating as it does the disadvantages of two injections. RENCZ (1936) tried to solve the problem by using two tubes. After exposing a film with the first tube, a mechanized cassette changer brought a second film into position to be exposed by the other tube. A stereoscopic pair of films could be obtained with this arrangement, the interval between the two exposures being 0.5 sec. The disadvantage of this method was that only one pair of films could be obtained, and the time interval between them was so great that the degree of vascular filling was changed sufficiently as to interfere with stereoscopic viewing. Modern apparatus for rapid film-changing have removed this objection to stereoangiography. After small adjustments, the Elema film-changer was found capable of posing pairs of roentgenograms with as small an interval as 0.17 sec between each film and with an interval of any chosen duration between the pairs. One or more pairs in each of the arterial, capillary, and venous phases, may thus be obtained during arteriography, the stereoscopic pair being almost identical in vascular phase.

The major problem has been to place the two alternately exposing roentgen tubes close enough to each other. In accordance with well-known facts, the ideal stereo-angle was found to be about 6 degrees, with resolving capacity for fine structures still maintained up to 12 degrees. The diameter of the casings of the ordinary tubes was too large

Submitted for publication, 7 April 1955.

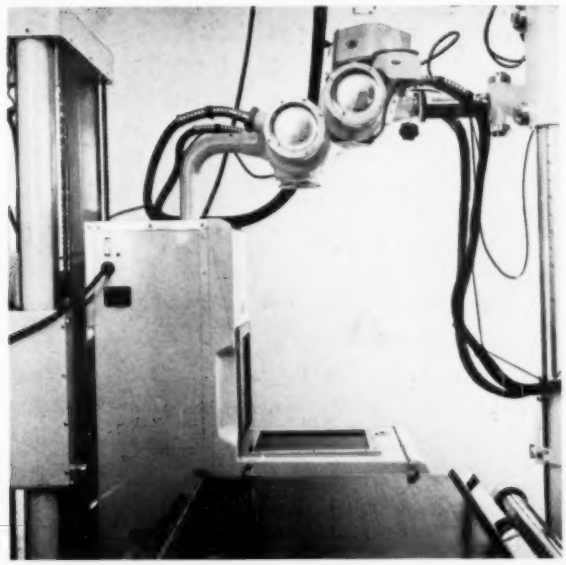

Fig. 1. Film-changer and the two roentgen tubes adapted for making serial stereoscopic exposures, with film—focus distances 90 and 102 cm, respectively. The angle between the central rays is 10°.

to permit of this angle between the roentgen beams at the usual focus—film distance (about 90 cm). This difficulty may be overcome if one tube is placed about 10 cm above and then as close to the other as possible; the tube apertures may then be arranged to give an angle of 10° between the roentgen beams (Fig. 1).

A series of test films was made with one tube maintained at a 90 cm focus—film distance with the other tube at various positions from 2 to 12 cm higher than the first, with a constant 10° angle between the beams. The stereoscopic effect was not influenced by small differences in distance and was still well maintained at 12 cm. The difference in distortion between the individual films was negligible. If desired, the effect of one slightly smaller image may be neutralized by placing the film affected slightly nearer the observer during the stereoscopic viewing.

As a result of these findings, the arrangement of the tubes as shown in Fig. 1 was employed.

A stereoscopic pair of films taken from the arterial phase of an aortogram are reproduced in Fig. 2. These demonstrate how little the vascular filling changed during the 0.17 sec interval between the exposures.

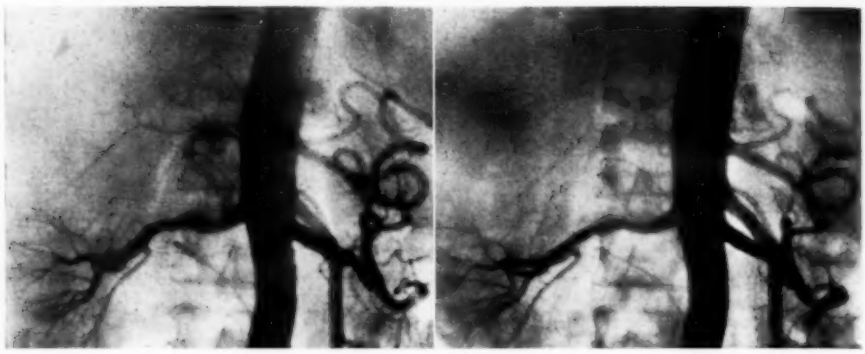

Fig. 2. Aortogram. Stereoscopic films, with a time interval of 0.17 sec between exposures. Note the absence of significant difference in vascular filling; this permits satisfactory stereoscopic viewing.

SUMMARY

Simultaneous stereoangiography performed by means of a rapid film-changer is described and discussed.

ZUSAMMENFASSUNG

Die simultane Stereoangiographie mit Hilfe einer schnellen mechanischen Film-Auswechslung wird beschrieben und diskutiert.

RÉSUMÉ

Description et discussion de la stéréo-angiographie simultanée réalisée au moyen d'un changeur de film rapide.

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SECONDARY REACTIONS FROM CONTRAST MEDIA AND THE ALLERGY CONCEPT

by

Carl Sandström

In an earlier paper the author has made certain observations concerning the secondary reactions which sometimes occur when contrast medium is injected into blood vessels. The toxicity of different contrast media, the frequency of secondary reactions, and their differential diagnosis and treatment, were the subjects primarily considered in that paper. Due to the continued development of roentgen diagnosis it is necessary that the problem of the influence of contrast media on the organism is subjected to intensified research. Clarifying investigations regarding the reason for, and the manner of origin of, these secondary reactions are still lacking. The exceedingly difficult maze of problems includes, among others, one question which I shall attempt to answer below, namely, whether the secondary effects are really caused by an allergic reaction of the organism against the contrast medium — as generally assumed. The investigation is based on observations of my own expanded material of urographies. The secondary reactions to be treated here are thus those of a more general character which occur in connection with the intravenous injection of a contrast medium in doses generally used in urographies. The discussion will, however, not include secondary reactions that may occur as a result of too high concentration of contrast medium in a certain vascular area, as demonstrated by experimental investigations in animals, such as brain injuries in cerebral angiographies (BROMAN and OLSSON), injuries of the spinal cord in aortographies (HOL and SKJERVEN), and kidney injuries in renal angiographies (IDBOHRN and BERG).

Submitted for publication, 10 January 1955.

HORSTERS was probably the first to consider the secondary effects as being due to an allergic reaction. In 1931, he published a case of cessation of breathing following injection of the contrast medium Abrodil, caused, in his opinion, by anaphylactic shock.

In 1939, HULTBORN published a number of cases of secondary reactions in urography, which also were assumed to be allergic reactions to the contrast medium. This theory has later been accepted by a number of research workers (v. BRAUNBEHRENS, ALYEA and HAINES, DOLAN, ROBINS, NATERMAN and ROBINS, O. OLSSON, PÄSSLER). PENDERGRASS et coll. consider that deaths in connection with the injection are caused by an anaphylactic or anaphylactoid hypersensitivity reaction due to an allergy in the patient to the contrast medium in question. CREPEA et coll. point out that the evidence of an allergic origin is not convincing, at least as far as some of the secondary reactions are concerned, but still maintain that the allergy hypothesis rests on a sounder basis in cases of immediate and serious dyspnoea, or collapse, in connection with the injection. The final proof that the secondary reactions are of an allergic character — the demonstration of the presence of antibodies against the contrast medium in the organism in those cases which have shown reactions — is, however, still lacking.

The term allergy is today used both in a narrower sense to denote certain conditions, such as asthma and hay fever, which are caused by, or assumed to be, the result of the influence of certain substances on the organism, and also in a wider sense for a great many different states of hypersensitivity, which arise, for example, during various infections and after the use of certain drugs, so-called drug allergy. Secondary reactions after the injection of contrast media belong to the latter category.

It is characteristic of drug allergy that only a small amount of the drug is required to bring about symptoms. This small amount causes no effect on non-allergic subjects (TAUB). Drug allergy is in most cases acquired, and is generally not combined with other manifestations of allergy. Repeated introduction of the drug causes, according to HANSEL, increased hypersensitivity and may thus bring on reactions of the most severe kind. The presence of even the slightest sign of an allergic reaction must therefore be a warning against the further introduction of the medium (HANSEL). Drug allergy is furthermore specific, in that the symptoms are released only by a certain substance or chemical group.

The origin of the allergic phenomena has been explained as being due to the drug combining with one of the albumins of the body and forming a so-called contrast medium complex (HABERSTUMPF). This new combination, the so-called 'hapten' is supposed to be capable of producing antibodies against the medium in question. If such antibodies have formed, for example, at a previous urography, a further examination

with the same contrast medium will cause allergic reactions, that is to say, secondary reactions, to arise. SCHUBERT and others have expressed the opinion that what is encountered is a hypersensitivity reaction against iodine, which is part of the contrast medium, and against which antibodies may have been present in the organism, causing secondary reactions. This cannot, in my opinion, be correct since modern preparations do not contain free, but only compounded, iodine. Cases with proven hypersensitivity against iodine have in the author's material exhibited no secondary reactions during urography with Umbradil.

This generally accepted theory regarding the origin of allergic secondary reactions has had practical consequences in the examinations and also indicated certain principles in the treatment of any symptoms which may arise. In order to ascertain the possible presence of allergic hypersensitivity, certain preliminary tests have been suggested, such as the reaction of the conjunctiva of the eye (ARCHER and HARRIS), intradermal or subcutaneous injections (ROBINS), and small intravenous injections (DOLAN, JÖNSSON et coll.). Furthermore, anti-allergic drugs (antihistamines) have been recommended (GETZOFF, CREPEA et coll., MOORE and SANDERS, INMAN) both for preventive and therapeutic purposes in cases in which secondary reactions occur (PENDERGRASS). In order to prevent secondary reactions, OLSSON has proposed the use of a compound contrast medium (Dijodon D), in which an antihistamine agent is included.

Author's Material

In my earlier paper I reported experiences in a material consisting of 8,897 urographies, out of which 4,867 were made with Umbradil (iodopyracet) 35 %. Among the latter, more serious but transient secondary shock-like reactions were observed only in two cases (0.04 %). In two other cases, prolonged vomiting occurred, lasting for about 15 minutes after the injection. In 8 cases (0.16 %) a pronounced rash, similar to urticaria, developed, disappearing only after 3 to 24 hours.

Due to these excellent experiences with Umbradil, this contrast medium has continued to be used in my Department in doses of 20 to 40 ml of the 35 % solution. The injection technique used is described in my previous paper. A total of 7,104 urographies have been made with this medium to date. One more case of secondary reactions of a serious nature has been observed, consisting of a shock-like state immediately after the injection (0.04 % of the entire material), and three cases of more pronounced reactions of the skin and mucous membranes, disappearing within 3 to 24 hours (0.15 % of the entire material).

In accordance with the principle laid down in my previous paper, care has always been taken to ensure that only slight compression is applied across the abdomen in order to prevent the development of what may be called the abdominal pressure syndrome. This includes the milder symptoms such as pallor, nausea and vomiting and severe and alarming signs such as a shock-like condition with low brachial blood pressure, increased heart rate, and unconsciousness. Since such symptoms, which almost immediately disappear as soon as the pressure is released, may occur in some subjects with even a small degree of compression, they may easily be falsely interpreted as secondary reactions caused by the contrast medium.

In employing the dosage mentioned of the contrast medium we never encountered any symptoms of renal reactions nor noticed that manifest signs in cases of renal disorders were increased. In spite of these observations we have avoided urography in cases with more advanced parenchymatous injury of the kidneys, in line with views expressed from other centres. Urography is considered to be a method of little diagnostic value in such cases.

Asthma and other so-called allergic conditions as well as hypersensitivity against iodine have not been considered to constitute contraindications. Furthermore, cases which during a previous urography with Umbradil have had slight or more serious secondary reactions, have been repeatedly subjected to the same contrast medium in the same dose in repeat examinations. Preliminary tests were formerly carried out in the Department in order to show whether any hypersensitivity existed, but in recent years such tests have been made only occasionally and merely for research purposes; the tests have been performed the day before the examination.

The Origin of Secondary Reactions. In order to answer the question posed — whether the secondary reactions are of an allergic character or not — support for the theory of allergy as well as certain factors which seem to disprove it, both based on observations in this material, will be presented. The evidence for and against the theory will be balanced and conclusions drawn.

A necessary postulate for an investigation of this kind is that one and the same contrast medium, having a constant chemical composition, is used throughout, the reason for this being that drug allergy is supposed to be caused by a specific substance or chemical group. For a number of years, I, for my part, have used only the contrast medium Umbradil, diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid.

The following observations support the allergy theory. The secondary reactions occur in immediate connection with the injection of the contrast medium. They are abnormal reactions, corresponding to the so-called allergic phenomena which have been described in cases of drug allergy. The symptoms and signs take the form of reactions of the skin

and mucous membranes and may vary from slight discomfort, such as itching of the skin of the face, irritation of the conjunctivae, sneezing, and a rapidly transient rash similar to urticaria, to graver manifestations such as edema of the face and glottis, etc. In certain cases, general reactions, described as anaphylactic or as allergic shock, may occur (ABDERHALDEN), that is to say a fall in the blood pressure in combination with a more or less pronounced state of shock.

The secondary reactions are also similar to allergic symptoms in that they follow the same development and are therapeutically affected by such drugs as adrenaline and calcium.

The following observations tend to disprove the theory.

1) Secondary reactions appear also in patients in whom contact with the contrast medium in question may be eliminated. According to the literature, drug allergy is supposed to be an acquired condition caused by an earlier administration of the same substance. An inherited allergy against the contrast medium is naturally out of the question.

2) No sensitization has been observed in repeated urographies on the same patient. Out of the author's own material, repeat examinations have been made in 1,557 cases (Table I) from twice to 10 times and with a time lapse between the first and last examination varying between 1 hour and 6 years. In none of these examinations have any symptoms suggesting definite indications of sensitization appeared. In Cases 4 and 6, summarized below, symptoms which might have been interpreted as being due to sensitization by the contrast medium were present; later urography, however, produced no confirmation of this.

Table I

Number of urographies on each patient	Number of patients	Shortest and longest time lapse between first and last injection
2	905	1 hour to 6 years
3	295	3 days to 4 years
4	164	20 days to 5 years
5 to 8	192	4 months to 5 years
10	1	5 years

3) Cases with secondary reactions during an earlier examination have, in one or more repeat examinations, generally had the same, or slighter symptoms, or none at all.

The following cases may be quoted:

Case 1. Female, aged 42, with attacks of pyelitis. *Urography:* 1951. 20 ml Umbradil. After 5 minutes general, urticarial type of rash and hoarseness. *Urography II:* 1952. 20 ml Umbradil. No secondary reactions.

Case 2. Male, aged 32. Examined for possible renal calculi. *Urography:* 1951, April. 40 ml Umbradil. Extensive skin reaction of urticarial type with large infiltrates. *Urography II:* May. 40 ml Umbradil. No reaction.

Case 3. Male, aged 62. Tumour of the bladder. *Urography* (performed at Södersjukhuset): 1949. 40 ml Umbradil. According to records of that hospital the patient was hypersensitive to the contrast medium and reacted violently with a severe shock-like condition immediately following the injection. *Urography II:* 1951. 40 ml Umbradil. Slight urticarial type of rash; otherwise no secondary reactions.

Case 4. Male, aged 32. Attacks of renal calculi. Urographies I—IV: 1948—50. 20 ml Umbradil each time. *Urography V:* 1951. 20 ml Umbradil. Shock-like state immediately after the injection. *Urography VI:* 1952. 20 ml Umbradil. No reaction.

Case 5. Male, aged 45. Probably old venous thrombosis. *Urography* with simultaneous *venography:* 20 ml Umbradil. General condition slightly affected, violent vomiting. After 60 minutes' rest the examination was repeated: 20 ml Umbradil. No reaction.

Case 6. Male, aged 44. Renal calculi. *Urography:* 1945, April. 20 ml Umbradil. No secondary reactions. Retrograde *pyelography:* 1945, Nov. 10 ml Umbradil. No secondary reactions. *Urography II:* 1951. 20 ml Umbradil. No secondary reactions. *Urography III:* 1951. 18 ml Umbradil. Two minutes after the start of the injection and before its completion a severe state of shock — pulse hardly palpable, loss of consciousness, and low blood pressure. The condition was rapidly relieved after injection of adrenaline. Violent vomiting on regaining consciousness. 1952: As preparation for further urography, the following tests were made. Eye test (20 Feb.) negative. Intracutaneous injection of 1 ml Umbradil 35 %: redness to a diameter of about an inch around the injection site. Subcutaneous injection of 0.5 ml Umbradil (21 Feb.). no reaction. It was decided to proceed with the urography, but at the patient's request it was not carried out. 1954: Eye test negative; intracutaneous injection of 0.1 ml c. m. negative; subcutaneous injection of 0.5 ml c. m. negative. *Urography IV:* 20 ml Umbradil. No secondary reactions caused by the contrast medium. After the compression had been applied the general condition was slightly affected, but this disappeared as soon as the compression had been removed and 1 ml ephedrine injected.

Cases 1 and 2 of the above had reactions of the skin and mucous membranes at the first examination, but not at those which followed. In Cases 3, 4, 5 and 6, there was a general reaction, partly of a shock-like character, which did not return when the urography was repeated. Cases 4 and 6 are interesting because the reaction did not occur until the 4th and 3rd (+ 1 pyelography) injection respectively. The reactions in these cases could easily have been misinterpreted as due to sensitization to the contrast medium as a result of former examinations. Since, however, a repeat injection of the same contrast medium in these patients caused no reaction, this indicates that there could have been no sensitization. In an additional 5 cases, reactions of the skin and mucous membranes were present in all examinations (2 urographies each in 2 cases; 3 in 3 cases). The degree of the reactions varied from time to time, but no pronounced intensification of the secondary reactions from the first to the last examination could be demonstrated.

In the following case, secondary reactions in the form of violent vomiting occurred in two urographies, but did not recur at a third examination.

Case 7. Male, aged 51. Chronic nephritis with decreased renal function. *Urography:* 1951, Aug. 20 ml Umbradil. Nausea and repeated vomiting. *Urography II:* 1952. March. 15 ml Umbradil. Same reaction. *Urography III:* Sept. 20 ml Umbradil. Slight nausea but no vomiting.

4) Preliminary skin or mucous membrane tests to ascertain the possible presence of allergic hypersensitivity conditions have proved to be of no value in indicating possible secondary reactions in individual cases (CREPEA et coll., SANDSTRÖM). This is also the reason why preliminary tests, which formerly were made as a matter of routine, have now been discarded before urography in my Department; it should, however, be observed that negative results of such tests constitutes no proof of the absence of drug allergy (CRIEP et coll.).

As examples of the many cases in which the preliminary tests have proved to be unreliable, the following may be cited:

Case 8. Male, aged 49. Examined for possible renal calculi. *Preliminary tests:* Eye test, no reaction. Intracutaneous injection of 0.1 ml c. m., no reaction. Subcutaneous injection of 0.5 ml, no reaction. *Urography:* 40 ml Umbradil. After 5 minutes a pronounced urticaria-like rash with edema of the lip and nostrils.

In this case of negative preliminary tests, there was thus a strong general reaction following the main injection.

Case 9. Male, aged 60. Hypertrophy of the prostate gland. *Preliminary tests:* Eye test, no reaction. Intracutaneous injection of 0.1 ml c. m., no reaction. Subcutaneous injection of 0.5 ml c. m., subcutaneous edema the size of a mandarin surrounding the site of injection and disappearing after about 4 hours. *Urography:* 20 ml Umbradil, no reaction.

There were thus no secondary reactions in this case, in spite of the fact that there had been a strong local reaction in one of the preliminary tests.

Case 5 may also be quoted in this connection as proof of the small value of preliminary tests. The first injection of contrast medium may here be considered to be in the nature of a preliminary test which was strongly positive. A further injection of the same contrast medium a short while afterwards caused, however, no reaction whatever.

Case 6 had a temporary positive reaction. Intracutaneous test on 20 February 1952 gave a positive reaction. Two years later the same test produced a negative result.

5) The author's material does not indicate that secondary reactions are more common among patients whose history includes previous allergic reactions than in those with no such record. Statistical material to support

this contention is, however, not available. In cases of asthma, iodine hypersensitivity, and other so-called allergic conditions, no secondary reactions have been observed. In cases in which more pronounced secondary reactions occurred, there had been no previous allergic reactions. Concerning this last point it should, however, be mentioned that drug allergy is held to be possible in individuals who have had no allergic reactions previously.

Summarizing the evidence that the appearance of secondary reactions is due to allergy, we find that the only fact supporting this theory is the conformity of the secondary reactions with allergic manifestations in the symptomatic picture and the history and duration of individual symptoms. The facts produced which disprove any allergic origin seems to the author to be so strong as to constitute direct evidence against the theory. There is no support for the theory that the contrast medium acts as an antigen, producing antibodies and that the side effects of the contrast medium thus is an antibody-antigen reaction. The author must therefore conclude that secondary reactions have nothing to do with the allergy concept, neither in its wider nor in its narrower sense (drug allergy).

What, then, is the nature of the secondary reactions? It seems possible to explain them as being, at least partly, toxic reactions to the contrast medium on the part of the organism. The chemico-physical properties of the contrast medium are in this connection of great importance. It is well known that secondary reactions are more common, and also more serious, with certain contrast media than with others, and that these depend upon the chemical composition of the respective contrast media. Certain observations indicate, however, that in addition one or more factors in the organism contribute in causing or releasing these secondary reactions. This subject will be more fully dealt with in a subsequent paper.

It seems interesting and noteworthy that it is possible by the injection of a contrast medium to cause secondary reactions so similar to allergic phenomena as to be mistaken for them, despite the fact that their cause has apparently nothing to do with allergy. It therefore appears likely that through continued investigations of the secondary reactions caused by contrast media as well as by other substances injected into the blood stream, one may also be able to make observations of value in the clarification of the cause of allergic phenomena and the mechanism of their origin.

SUMMARY

On the basis of experiences gained from a material of 1,557 cases, where urographies with one and the same contrast medium (Umbradil) were carried out from two to ten

times on the same patient, the author comes to the conclusion that the secondary reactions, caused by the injection of contrast media into the blood stream, are not of an allergic nature, as generally assumed in the literature.

ZUSAMMENFASSUNG

Auf Grund der Erfahrungen aus einem Material von 1,557 Fällen, in denen Urographien mit ein und demselben Kontrastmittel (Umbradil) bei jedem Patienten 2—10 mal ausgeführt wurden, kommt der Verfasser zu dem Schlussatz, dass die Nebenerscheinungen, welche durch die Injektion des Kontrastmittels in den Blutstrom verursacht werden, nicht allergischer Natur sind, wie es in der Literatur allgemein angenommen wird.

RÉSUMÉ

Se fondant sur l'expérience acquise sur un matériel de 1,557 cas d'urographies faites avec un même et unique produit de contraste (Umbradil) de deux à dix fois chez le même malade, l'auteur arrive à la conclusion que les réactions secondaires dues à l'injection de produits de contraste dans le courant sanguin ne sont pas de nature allergique, une opinion contraire à celle exprimée dans la littérature.

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FROM THE INSTITUTE OF GENERAL AND EXPERIMENTAL PATHOLOGY (DIRECTOR: PROF. LEIV KREYBERG), UNIVERSITY OF OSLO, NORWAY

THE EFFECT OF CYSTEAMINE, CYSTAMINE AND HYPOXIA ON MORTALITY AND BONE MARROW CHROMOSOME ABERRATIONS IN MICE AFTER TOTAL BODY ROENTGEN IRRADIATION

by

Finn Devik and *Francis Lothe*

It has been well established that various chemical agents, if present during irradiation, can protect against roentgen irradiation damage (GRAY 1951, and PATT 1953, 1954). It is especially the thiol compounds that have been found to be effective, and of these cysteine has most frequently been employed in experiments.

Cysteine has been shown to protect against radiation-induced chromosome aberrations, for instance, in the cells of onion root tips (MIKAELSEN 1952, FORSSBERG and NYBOM 1953) and in the bone marrow cells of mice (DEVIK 1954).

BACQ found that cysteamine (beta-mercaptoethylamine, 'Becaptan' Labaz) showed a greater protection against death following roentgen irradiation than cysteine (1952), and he suggested (personal communication) that DEVIK's studies on bone marrow chromosomes in mice be repeated with this compound given prior to exposure. This has been the object of the present experiments.

Materials and methods

Fifty- to eighty-days-old male albino mice were used in the experiments. In each set of experiments, WLO mice of the same age and weight (18 to 22 grams) and from the same stock boxes were used. Test and control animals were always treated simultaneously.

The chemicals were injected intraperitoneally 8 to 12 minutes prior to irradiation. In order to obtain a maximum effect, doses just short of being toxic were employed.

Submitted for publication, 23 February 1955.

A quantity of 3 milligrams of cysteamine or 5 milligrams cystamine in 0.2 ml distilled water was found to be suitable (150 and 250 mg/kg body weight). In some experiments, cysteine was given, the dose being 10 milligrams cysteine hydrochloride dissolved in 0.2 ml distilled water and neutralized by sodium hydroxide. As cysteamine is unstable in solution in the presence of oxygen, the dilutions employed were freshly made up each time, and on several occasions their strength was checked by iodine titration.

A moderate hypoxia was induced in some of the animals by passing 8.45 per cent oxygen in nitrogen through one half of the box containing the mice. Oxygen was passed through the other half of the box which was separated from the first by an air-tight dividing panel. In both halves there were holes to allow the gas to escape freely. The gases were passed through the box for two minutes prior to irradiation and throughout exposure.

The mice were kept in thick-walled Perspex boxes during irradiation. The physical conditions were: 170 kV, 15 mA, 1 mm Cu filter, HVL 1.2 mm Cu, distance from target to the middle of the box 42 cm, dose-rate 37 r/min. Twelve mice were irradiated simultaneously, the dose being 200 r. To be able to deliver lethal doses in a relatively short time, the following physical conditions were used: 190 kV, 15 mA, 0.5 mm Cu filter, HVL 0.85 mm Cu, distance from target to the middle of the box 22 cm, dose-rate 387 r/min. Six mice were irradiated simultaneously, the dose being 1,100 r. All irradiation was carried out at the same time of the day, *i. e.* from 2.30 p. m. to 4 p. m., in order to reduce the possible effect of diurnal variations in the number of mitoses (Bullough 1948).

In the bone marrow, chromosome aberrations were used as an early and sensitive indicator of the degree of irradiation damage. The radiation-induced chromosome breakages partly result in loose fragments and partly in dicentric bridges, both of which are readily observed in the anaphase of cell division. A percentage count of the normal and abnormal anaphases may thus give some quantitative measure of the damage.

The bone marrow was prepared by the squash technique and stained by Feulgen's method, as in previous experiments (Devik 1952). Fifty anaphases were counted in almost all preparations. The analyses were carried out without knowing which slides were from test animals and which from controls, or the time of fixation, except in the case of the preparations fixed 18 hours after irradiation, when the time of fixation was known.

Results

In preliminary experiments on mortality the protective effect of cysteamine and cystamine was compared with that of cysteine (Table I). With the present experimental conditions and criteria, the three substances are seen to have approximately the same protective effect. This effect is increased when the animals are exposed to moderate hypoxia during irradiation.

Table I

The fraction of mice alive 30 days after 1,100 r of total body irradiation. The numerator denotes the number of mice surviving and the denominator the number irradiated. The figures are made up from two identical sets of experiments

Given prior to irradiation	Untreated controls	Cysteine 10 mg	Cysteamine 3 mg	Cystamine 5 mg
Irradiated in atmosphere rich in oxygen...	$\frac{0}{20}$	$\frac{1}{20}$	$\frac{3}{19}$	$\frac{2}{21}$
Irradiated in 8.45 per cent oxygen.....	$\frac{4}{20}$	$\frac{12}{19}$	$\frac{12}{17}$	$\frac{13}{18}$

Table II shows the effect of cysteamine and cystamine on the number of abnormal mitoses in the bone marrow 18 hours after 200 r total body irradiation. It is seen that both substances reduce the percentage of abnormal anaphases, and that this effect is increased when the animals are exposed to moderate hypoxia during irradiation. Although the influence of cystamine does not appear very convincing, the fact that the addition of hypoxia increases this beyond that of each one separately is in favour of a protective effect of cystamine.

Table II

The percentage of abnormal anaphases in bone marrow of mice with and without the presence of cysteamine, cystamine and hypoxia during roentgen irradiation. The results are the average of two sets of identical experiments, each figure representing 15 to 17 mice. Counts were made 18 hours after exposure to a dose of 200 r total body irradiation

	Controls	Cysteamine 3 mg	Hypoxia	Cysteamine 3 mg + hypoxia
Abnormal anaphases (%)	61	41	57	37
Difference		20	4	24
Probability		0.05—0.1	> 0.4	0.2—0.01

	Controls	Cystamine 5 mg	Hypoxia	Cystamine 5 mg + hypoxia
Abnormal anaphases (%)	63	55	56	40
Difference		8	7	23
Probability		0.4	> 0.4	0.05—0.1

To make sure that the analysis 18 hours after irradiation gave a representative picture of the whole process, preparations were also fixed at intervals varying from $1^1/_2$ min to 51 hrs after irradiation. Half the animals were given cysteamine prior to irradiation and the remaining half used as controls. A small number of preparations were made at frequent intervals rather than a greater number at less frequent intervals. In addition to the percentage of abnormal anaphases, the number of mitoses from pro- to telophase per 1,000 cells (mitotic index) and the number of degenerate cells per 1,000 were counted. Only cells with nuclei of a structureless homogeneous appearance were counted as three experiments. The main experiments with fixation after 18 hours degenerate. The results are shown in Diagram 1, which is made up from are included in addition. It is seen that the percentage of abnormal anaphases rises rapidly after irradiation and then gradually decreases, the percentage being lower in the cysteamine treated animals, at least during the first 24 hours. The cysteamine has no striking effect on the mitotic count. Degenerate cells suddenly appear in increased numbers about two hours after irradiation, and disappear again almost completely after some hours.

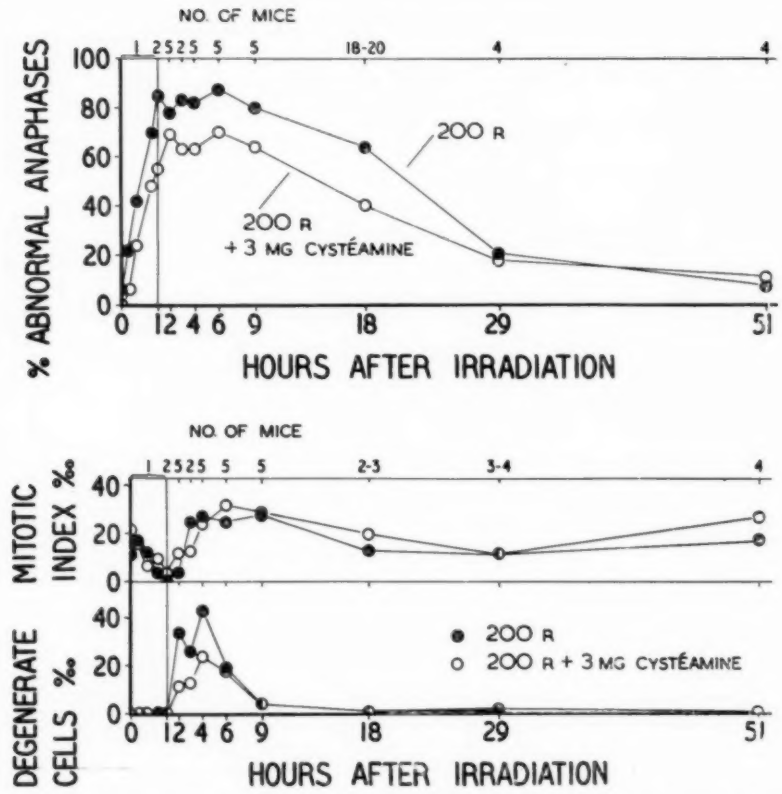

Diagram 1. Upper graph: The percentage of abnormal anaphases in the bone marrow of mice following 200 r total body irradiation, with and without administration of cysteamine prior to exposure. Fifty mitoses were recorded in each preparation, except in those with a low mitotic index. Lower graph: The mitotic index and the number of degenerate cells per 1,000 cells in the same preparations.

Discussion

The experiments show that cysteamine and cystamine can to some extent protect against radiation-induced chromosome damage in bone marrow of mice. It is of interest to note that this type of damage may already be observed during the first hour after moderate doses of irradiation, and the protective effect of cysteamine seems already to manifest itself at this stage.

It is possible that some of the early changes after irradiation are due to 'stickiness' and not to genuine chromosome aberrations, as the cells

are small and it may be difficult to distinguish between the two. The changes observed do not, however, seem to differ in any particular way from those observed later.

The cytologic changes in bone marrow of mice after total body irradiation show many similarities with those described in irradiated tissue cultures (SPEAR 1948). In both cases there is a considerable mitotic depression after irradiation with moderate doses followed by a more or less compensatory increase. Abnormal mitoses with chromosome aberrations are found in both. Degenerate cells also appear in both cases. In tissue culture the latter are partly associated with abnormal mitoses and partly they degenerate without undergoing mitosis (LASNITZKI 1943). In rats receiving large doses of irradiation, the number of cells in the bone marrow falls so rapidly (BLOOM 1948) that it cannot be explained only by cell death following abnormal mitosis.

In the present experiments the degenerate cells have a different distribution in time than the abnormal anaphases and the compensatory increase in cell division, which is in accordance with the view that degeneration may occur independently of mitosis.

Excitation alone may, in certain cases, cause a depression of mitosis. FRIEDENWALD and BUSCHKE (1944) reported a depression of nearly a hundred per cent in the rat cornea one hour after excitation by pinching the tail, loud noises, injection of saline, or after injection of epinephrine. They found a much less pronounced depression in the bone marrow. To investigate the possible effect of excitation induced in the present experiments, 12 mice were manipulated as in the experiments, 6 were irradiated, and bone marrow from all the mice fixed one hour later. On analysis, the non-irradiated mice averaged 20 and the irradiated ones 3 mitoses per 1,000 cells. Six mice which were taken directly from the stock boxes at the same time showed a mean mitotic index of 20.

Acknowledgements

One of us (F. D.) acknowledges his indebtedness to 'Landsforeningen mot Kreft' for the grant of a Research Fellowship, and the other (F. L.) to 'C. H. Homans Legat og Legatet til Henrik Homans Minde' and 'Statssekretær Jacob Aall og hustrus legat' for financial support.

Société des Laboratoires 'Labaz' (Brussels) kindly placed cysteamine and cystamine at our disposal.

SUMMARY

A total of 154 mice were subjected to 1,100 r and 110 mice to 200 r total body irradiation following the administration of cysteamine or cystamine in order to gauge the protective properties of these substances against irradiation damage. With the former dose, death of the mice was the indicator of damage while, with the latter dose, chromo-

some aberrations in the bone marrow were evaluated quantitatively. In both series, the chemical compounds showed a protective effect which was increased when hypoxia was induced prior to and continued during the exposure.

ZUSAMMENFASSUNG

Insgesamt 154 Mäuse erhielten 1,100 r und 110 Mäuse 200 r Totalbestrahlung im Anschluss an die Verabreichung von Zysteamin oder Zystamin mit der Absicht, die Schutzeigenschaften dieser Substanzen gegen Strahlenschädigungen zu beurteilen. Mit der erstgenannten Dosis wurde der Tod der Mäuse als Indikator für die Schädigung benutzt, bei der letzteren Dosis wurden die Chromosomenveränderungen im Knochenmark quantitativ bewertet. In beiden Serien zeigten die chemischen Verbindungen eine schützende Wirkung. Diese wurde gesteigert, wenn eine Hypoxie vor der Bestrahlung eingeleitet und während derselben fortgezetzt wurde.

RÉSUMÉ

Un lot de 154 souris a été soumis à 1,100 r et un lot de 110 souris à 200 r en irradiation de tout le corps, après administration de cystéamine ou de cystamine, pour évaluer les propriétés protectrices de ces substances à l'égard des radiolésions. Pour la première dose, la mort des souris a servi à apprécier les lésions; pour la seconde, les aberrations chromosomiales de la moelle osseuse ont été évaluées quantitativement. Dans les deux séries, ces composés chimiques ont présenté un effet protecteur qui était augmenté quand on créait une hypoxie avant et pendant l'irradiation.

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MODIFICATION DE LA RADIOSENSIBILITÉ DU RAT PAR HYPOTHERMIE PROFONDE

par

S. Hajdukovič

Les nombreuses expériences faites dans le but d'éclaircir le problème de l'influence des températures basses sur la radiosensibilité des êtres vivants ont donné des résultats contradictoires. La plupart des auteurs ont utilisé des organismes unicellulaires, des tissus ou organes isolés ou des poïkilothermes. La réponse des homéothermes a été beaucoup moins étudiée.

Nous avons étudié chez le rat l'action d'une hypothermie profonde réalisée pendant le temps nécessaire à l'administration d'une dose mortelle de rayons roentgen.

Matériel expérimental et méthode

Les homéothermes peuvent être amenés en hypothermie soit par immobilisation et immersion dans l'eau glacée, soit par asphyxie et refroidissement, conditions dans lesquelles l'animal abaisse très vite sa température corporelle (DJAJA 9, 10). Nous avons employé ce procédé parce qu'il est simple et qu'il ne provoque pas de troubles visibles chez les animaux après le réveil de l'hypothermie. Cette méthode a été décrite en détail dans l'étude de l'influence de l'hypothermie sur le fonctionnement de la glande thyroïde chez les homéothermes (37), et les diverses techniques que nous avons utilisées ont fait l'objet d'un exposé détaillé dans une précédente publication (14).

Dans ce travail, nous avons employé des rats des deux sexes, d'un poids de 130—150 g. Les animaux ont été irradiés lorsque la température rectale était de 14—15° C.

Conditions d'irradiation: Appareil Picker 250 kV, 18 mA, filtre 0.25 mm Cu, distance focale 50 cm, champ d'irradiation 10 × 10 cm, intensité 80 r/min, temps d'irradiation 10 min. Pendant l'irradiation les animaux sont installés dans une boîte en carton. La dose d'irradiation a été mesurée par un dosimètre «Universal» Siemens. Pour nos animaux, une dose de 800 r est 100 % mortelle en 17 jours.

Après l'irradiation, les rats sont laissés à la température de la chambre. Nous avons observé les animaux pendant 30 jours.

Soumis à la Rédaction le 28 Octobre 1954.

Résultats

Nous avons consigné nos résultats dans le tableau I, qui résume nos expériences. Nous avons procédé à divers essais:

1. Hypothermie avec asphyxie (tabl. I — 3, 4).
2. Hypothermie en présence d'oxygène (tabl. I — 5, 6, 7).
3. Hypothermie après surrénalectomie (tabl. I — 9).
4. Hypothermie après narcose au Nembutal (tabl. I — 8).
5. Hypothermie après irradiation seulement (tabl. I — 11).
6. Hypothermie avant, pendant, et 2 heures après l'irradiation (tabl. I — 12).
7. Hypothermie suivie de réchauffement au moment d'irradiation (tabl. I — 13).
8. Irradiation après 2 unités/kg d'insuline.

Tableau I

No	Nombre d'animaux	Expérimentations	T° rectale	Dose en r	Survie après 30 jours	Remarques
1	13	Témoins	37°C	800	0	morts en 15 jours
2	10	Témoins	37°C	900	0	morts en 12 jours
3	13	Hypothermie avec asphyxie	14—15°C	800	8	
4	9	Hypothermie avec asphyxie	14—15°C	900	5	
5	10	Hypothermie en présence d'oxygène	11—13°C	800	8	
6	8	Hypothermie sous pression de 1.25 atmosphère d'air	15°C	800	5	
7	10	Témoins irradiés sous pression de 1.25 atmosphère d'air	15°C	800	0	morts en 11 jours
8	7	Hypothermie après 0.18 mg de Nembutal	15°C	800	3	
9	6	Adrénalectomie — DOCA Hypothermie	15°C	800	0	mortalité ralentie
10	10	Insuline, 2 unités par kg	37°C	800	0	morts en 10 jours
11	6	Hypothermie après rayons roentgen	37°C	800	0	morts en 12 jours
12	9	Hypothermie maintenue 2 heures après rayons roentgen	17°C	800	0	morts en 11 jours
13	7	Hypothermie puis réchauffement avant rayons roentgen	37°C	800	0	morts en 15 jours

Nous avons d'abord expérimenté l'effet de l'hypothermie avec asphyxie qui donne, comme on le voit dans le tableau I, une protection non négligeable. Dans le but d'examiner l'influence de l'hypothermie sans hypoxie, nous avons monté un appareillage donnant un courant d'air continu à une pression constante de 1.25 atmosphère d'air pendant le refroidissement et l'irradiation. Dans ces conditions, la radioprotection par le froid s'exerce encore.

Le froid est un puissant excitant du système sympathicosurrénal. Pour diminuer la réaction de la surrénale et la sécrétion des amines (adrénaline et noradrénaline) dont Bacq et Herve (2, 3, 4, 5), Gray et coll. (13) ont constaté l'effet protecteur contre l'irradiation, deux

groupes d'animaux ont été anesthésiés au Nembutal, puis refroidis par asphyxie.

Un premier groupe de dix rats a reçu 0.30 mg de Nembutal par voie intrapéritonéale mais cette dose s'est montrée toxique pour les animaux refroidis car 7 d'entre eux moururent pendant le refroidissement ou l'irradiation. Un second groupe de dix rats a reçu 0.18 mg de Nembutal par voie intrapéritonéale; trois de ces animaux succombèrent pendant le refroidissement. Des sept animaux restants, irradiés par 800 r, trois étaient en vie 30 jours après l'irradiation.

Dans le même ordre d'idées, nous avons procédé à la surrénalectomie d'un groupe de rats recevant une injection biquotidienne de 2 mg de DOCA. Le sixième jour, 6 animaux ont été refroidis et irradiés à dose mortelle de rayons roentgen, en hypothermie profonde. L'hypothermie profonde ralentit la mortalité chez les rats adrénalectomisés et irradiés. L'hypothermie seule n'a aucune influence sur la mortalité des animaux adrénalectomisés. A noter que le refroidissement des rats surrénalectomisés est aussi long que celui des rats normaux, mais que le réchauffement après l'irradiation est beaucoup plus difficile.

Enfin, un autre groupe de dix rats a reçu, après une légère anesthésie au Nembutal, 2 unités/kg d'insuline afin de provoquer une décharge d'adrénaline. Trente minutes plus tard, les animaux ont été irradiés par 800 r. Tous ces animaux moururent dans les 10 jours suivant l'irradiation.

Nous avons examiné l'influence de l'hypothermie après l'irradiation et l'influence d'un réchauffement au moment même du traitement par rayons roentgen. Aucune protection n'a été observée dans ces deux cas.

Discussion

A. Généralités. L'influence d'une température basse sur les processus déclenchés dans l'organisme après l'irradiation par rayonnements ionisants a fait l'objet de nombreuses expériences. Les résultats se sont montrés peu concordants. Les conditions expérimentales souvent très différentes et la spécificité biologique des êtres vivants étudiés peuvent certainement expliquer certaines contradictions.

Nous avons résumé dans le tableau II les principales données bibliographiques relevées dans la littérature (depuis trente ans) sur le refroidissement *après* l'irradiation, et dans le tableau III l'effet de refroidissement *pendant* l'irradiation.

La plupart des organismes utilisés ont été des unicellulaires, des œufs ou des plantes. Seule, une infime minorité d'auteurs a étudié le comportement des mammifères, et une unique publication a trait aux homéothermes non hibernants.

Tableau II

Action du refroidissement après l'irradiation

Nombre du matériel examiné	L'effet de l'irradiation diminué	sans effet	augmenté
11	8	2	1

L'influence du refroidissement après l'irradiation diminue en général l'effet des rayons ionisants. Seule l'expérience de HENSHAW (15) ne s'accorde pas avec ce point de vue. Dans les travaux de SMITH et coll. (31—32), KIMELDORF et coll. (19) et BARLOW et coll. (6), l'augmentation de la mortalité peut être expliquée par des phénomènes indirects survenus à la suite de la manœuvre de refroidissement.

L'effet favorable du refroidissement appliqué après l'irradiation ne peut évidemment intéresser que les processus secondaires à la radiolésion dans le sens d'un ralentissement. Les travaux de COOK (8) et TAHMISIAN (35) sont très suggestifs. Le premier a montré que le nombre des embryons anormaux était très réduit sous l'influence du refroidissement et le second que les doses de 2,500 r étaient sans aucun effet sur les œufs de sauterelle exposés, pendant six mois, à la température de 0° C, après l'irradiation. Il semble évident que le refroidissement pendant cette période a favorisé les processus de réparation des radiolésions.

Les résultats de l'effet du refroidissement pendant l'irradiation sont beaucoup plus discutés.

Tableau III

Action du refroidissement pendant l'irradiation

Nombre du matériel examiné	L'effet de l'irradiation diminué	sans effet	augmenté
32	15 (2 ralentic)	9	6

Il est difficile de supposer que le refroidissement influence le transfert d'énergie et l'échange de radicaux libres. Pendant l'irradiation elle-même, radiolésions et processus de réparation doivent être très voisins et l'on peut penser que le refroidissement agit davantage sur les réactions secondaires de la «période sombre».

Nous signalerons quelques points particuliers du tableau présenté.

1. Les expériences sur *Paramaecium* (11) et sur les spermatozoïdes de *Sphaerocarpus Donelli* (30) ont été effectuées avec des rayons ultraviolets dont le mode d'action est différent de celui des radiations ionisantes.

2. L'expérience de STAPLETON et coll. (33) sur *Escherichia coli* peut s'expliquer par le fait que ces auteurs ont irradié un milieu gelé.

3. Le refroidissement semble augmenter les altérations chromosomiques (36, 22, 24, 29) comme s'il empêchait le réarrangement des fragments.

4. Aux expériences faites sur la peau du rat et du lapin, on peut objecter l'influence du refroidissement sur la circulation locale. Les travaux de MOTTRAM (23), en contradiction avec les précédents, trouvent probablement une explication dans la technique utilisée (refroidissement insuffisant par l'eau glacée provoquant elle-même une augmentation de la circulation).

B. Résultats personnels. 1. Grâce à l'hypothermie profonde réalisée par notre technique, les animaux sont immobiles avec fort abaissement du rythme respiratoire et des contractions cardiaques. Les animaux sont irradiés dans cet état. Après l'irradiation, ils reprennent spontanément leur température normale en moins de 4 heures; on note une température rectale de 23.6° C après 2 h.30. A cette température, STORER et HEMPELMANN n'ont constaté aucune protection chez la souris. L'expérience que nous avons réalisée sur le rat maintenu à 17.5° et irradié à dose mortelle montre, par contre, une nette protection. Le maintien de l'hypothermie *après* l'irradiation supprime cette radioprotection. L'hypothermie réalisée *uniquement après* l'irradiation n'a pas plus de succès.

2. BACQ et HERVE (2, 3, 4, 5), GRAY et coll. (13) ont montré le rôle protecteur de faibles doses d'adrénaline et de noradrénaline que l'on sait être secrétées par la glande surrénale. D'après les expériences que nous avons faites (anesthésie au Nembutal, animaux surrénalectomisés ou en état d'hypoglycémie provoquée par injections d'insuline), la libération des amines de la glande surrénale n'explique pas la protection obtenue.

3. L'hypothermie profonde diminue le métabolisme et la quantité d'oxygène utilisé (DJAJA (9, 10), BIGELOW (7)). Elle déplace la courbe de dissociation de l'oxyhémoglobine à gauche; elle influence donc l'oxygénation des tissus en augmentant l'affinité de l'hémoglobine pour O_2. Mais, en même temps, d'autres facteurs s'opposent à ce phénomène. Pendant le refroidissement d'un homéotherme, le pH sanguin s'abaisse et ce phénomène tend à supprimer le phénomène de l'hypothermie sur la courbe de dissociation de l'oxyhémoglobine. KAYSER (18) a montré qu'un pH 6.8 était nécessaire à la température de 15° C, pour compenser le déplacement de la courbe. De plus, chez un animal en hypothermie, l'hémoconcentration visible à l'hématocrite favorise l'oxygénation des tissus, la vitesse de circulation est ralentie et l'oxygène dissous dans le plasma atteint une valeur nettement supérieure à celle

observée à 38° C. PENROD (28), BIGELOW et coll. (7) ont réalisé une hypothermie profonde de 18° C (mesurée dans le rectum; en dessous de cette valeur, le refroidissement devient critique chez le chien, comme en dessous de 15° C chez le rat) chez le chien et n'ont constaté aucune anoxie tissulaire pendant cette période:

a) il n'existe pas de chute anormale d'oxygène pendant le passage du sang à travers les tissus,

b) pendant le réchauffement spontané de l'animal, on n'observe pas d'augmentation brusque de la consommation d'oxygène; cette augmentation est linéaire en fonction de la température de réchauffement, ce qui semble pouvoir éliminer une anoxie antérieure,

c) la consommation d'oxygène ne change pas pendant une hypothermie s'étalant de 30 minutes à 4 heures,

d) on n'observe aucune séquelle (cérébrale par exemple) qui pourrait suggérer une anoxie importante et durable.

4. Il n'est pas possible de comparer les résultats obtenus chez les hibernants et les homéothermes non hibernants parce que les réactions de l'hémoglobine et les échanges gazeux sont tout à fait différents chez ces deux groupes d'animaux.

KAYSER (18) a trouvé que l'affinité de l'hémoglobine envers l'oxygène dans le sommeil hivernal était moins marquée que ne l'exigerait l'abaissement de la température interne. Même à la température de 8.6° C, les hibernants réussissent à libérer de sensibles quantités d'oxygène. Un homéotherme ne pourrait dégager ces dernières sans abaisser considérablement son pH sanguin.

Chez les hibernants, la mortalité, après irradiation aux rayons roentgen n'est pas diminuée, mais ralentie. Chez les homéothermes non hibernants, la mortalité est diminuée. Cette constatation peut-elle s'expliquer uniquement par l'utilisation plus difficile de l'oxygène sanguin? Nos expériences en présence d'oxygène et sous pression augmentée d'air sont plutôt en faveur de la thèse que le rôle protecteur du refroidissement interne ne s'explique pas par la seule anoxie. Nous admettons, à titre d'hypothèse de travail, que l'influence de l'hypothermie sur la protection des mammifères doit surtout être en rapport avec le niveau des processus métaboliques.

RÉSUMÉ

Il est montré que 50 % des rats irradiés en hypothermie profonde (température rectale de 14 à 15° C) par des doses léthales de 800 à 900 r survivent plus de 30 jours tandis que tous les témoins meurent en 17 jours. On obtient le même degré de protection si l'hypothermie est réalisée en présence d'oxygène ou sous une pression d'air de 1.25 atmosphère. Il est probable que l'influence de l'hypothermie sur la mortalité des mammifères irradiés soit en rapport avec le niveau des processus métaboliques et qu'elle ne soit pas due à l'anoxie seule.

SUMMARY

It was found that 50 % of rats, irradiated in the state of deep hypothermy (rectal temperature of 14—15° C) with lethal doses of 800 and 900 r, survived more than 30 days whereas all controls died within 17 days. The same degree of protection is obtained if the cooling is made in the presence of oxygen or under an air pressure of 1.25 atmosphere. It is likely that the influence of hypothermy on the mortality of roentgen-irradiated mammals is related to the general level of metabolic processes and not only due to anoxia.

ZUSAMMENFASSUNG

Von den im Zustand tiefer Hypothermie (Rektaltemperatur 14° bis 15° Celsius) mit letalen Dosen von 800 r und 900 r bestrahlten Ratten lebten 50 % länger als 30 Tage, während sämtliche Kontrolltiere innerhalb von 17 Tagen starben. Die gleiche Schutzwirkung wird erreicht, wenn die Abkühlung in einer Sauerstoffatmosphäre oder bei einem Luftdruck von 1.25 Atmosphären geschieht. Es ist anzunehmen, dass der Einfluss der Hypothermie auf die Mortalität röntgenbehandelter Säugetiere auf das allgemeine Niveau der Stoffwechselprozesse zurückzuführen ist und nicht nur auf der Anoxie beruht.

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PHANTOMMESSUNGEN ZUR BEWEGUNGSBESTRAHLUNG IM HALSGEBIET

von

Hans-Joachim Maurer

Obwohl die bisherigen Bestrahlungsmethoden der Tumoren des Larynx und Hypopharynx schon weitgehend festgelegt sind (20 und 27), erschien es doch interessant und auch zweckmässig, in Phantommessungen die Brauchbarkeit der verschiedenen Methoden der Bewegungsbestrahlung in dieser Hinsicht nachzuprüfen. Hierzu besteht umso mehr Anlass, als von verschiedenen erfahrenen Strahlentherapeuten immer wieder eingewandt wird, dass der Aufwand im Verhältnis zu der zu erzielenden Leistung doch recht gross sei (27).

Die nachfolgenden beschriebenen Messungen wurden zusammen mit F. KAULFERSCH durchgeführt, der in anderem Zusammenhang über weitere Einzelheiten berichten wird (9).

Methodik

Die Messungen wurden an zwei Paraffin-Magnesiumoxyd-Halsphantomen durchgeführt, die sich hinsichtlich ihres Umfanges: 11.7 bzw. 13.5 cm unterscheiden. Die Trachea wurde durch eine entsprechende Bohrung mit einem Durchmesser von ca. 2.0 cm dargestellt. Ferner wurden verschiedene Messkanäle (je 10 mm) angelegt, die bei Nichtbenutzung mit Plexiglasstäben verschlossen wurden (Abb. 2). Die Messungen wurden mit einem Siemens-Universaldosimeter und einer kleinen Fingerhutkammer (10.0 mm^3), die im Bereich der angewandten Strahlung (200 KV) weitgehend strahlungsunabhängig ist, durchgeführt.

An Geräten standen zur Verfügung:

1. Konvergenzstrahler (Siemens-Reiniger), dessen Ergebnisse an anderer Stelle besprochen werden sollen (9).
2. Pendelgerät nach KOHLER (Siemens-Reiniger) und
3. TU 1 (C. H. F. MÜLLER) bei dem sowohl reine Pendelung als auch die Pendelkonvergenz (H. WICHMANN) ausgemessen wurden.

Bei 2 und 3 wurden Pendelwinkel von 90, 100, 180, 240 und 280° benutzt (s. Abb. 2), bei der Pendelkonvergenz zusätzlich noch Translationswinkel von (± 10°) und (+ 15°—20°). Am Konvergenzstrahler wurden folgende Kombinationen verwandt: Herdfeldblende (Hfbl.) 6 und Abstandstubus (AT.) 7 bzw. Hfbl. 3 und AT. 5.

[1] Auszugsweise im Rahmen der Wintersitzung der Bayer. Röntgenvereinigung, Nürnberg, Dez. 1954, vorgetragen; bei der Red. am 20. Dez. 1954 eingegangen.

Abb. 1. Abbildung der beiden verwandten Halsphantome, links: 13.5 cm ∅ (»dicker Hals«), rechts: 11.7 cm ∅ (»dünner Hals«). Material: Magnesiumoxyd-Paraffin.

In den Abbildungen sind die angegebenen Werte auf das als 100 % gesetzte Dosismaximum bezogen. Die Feldgrössen beziehen sich auf die verschiedenen Herdfelder. Der schematische Horizontalschnitt liegt in Höhe von CV. Die Bestrahlungen wurden mit 200 KV, 20 mA und 0.5 bzw. 0.2 mm Cu-Filtern durchgeführt.

Ergebnisse

Abgesehen von der Pendelkonvergenz (PK) fand sich bei den anderen Methoden übereinstimmend, dass die aus den Tabellen entnommene Drehpunkt-bzw. Pendeltiefe tiefer lag als sie tatsächlich gefunden wurde: Drehpunkt- und Herdtiefe fielen stets zusammen, wie dies auch schon bei ähnlichen Messungen am kleinen Becken gefunden wurde (15, 16). Am Konvergenzstrahler lag bei entsprechend der Phantomherdtiefe gewählten Tubuskombinationen deren Dosismaximum ebenfalls tiefer als nach den beigegebenen Isodosen-Tabellen zu erwarten war.

Tabelle 1

Verhältnis der errechneten zu den gemessenen Drehpunkttiefen bei der PK eines »dünnen Hals«-Phantoms

Feldgrösse	Translat.-Winkel	Pendel-Winkel	Drehpunkttiefe für Max. in 4 cm Tiefe	
			errechnet	gemessen
2.5 × 5 cm	± 10°	± 45°	4.75 cm	4.5 cm
		± 90°	3.75 »	4.0 »
		± 120°	3.50 »	
		± 135°	3.12 »	

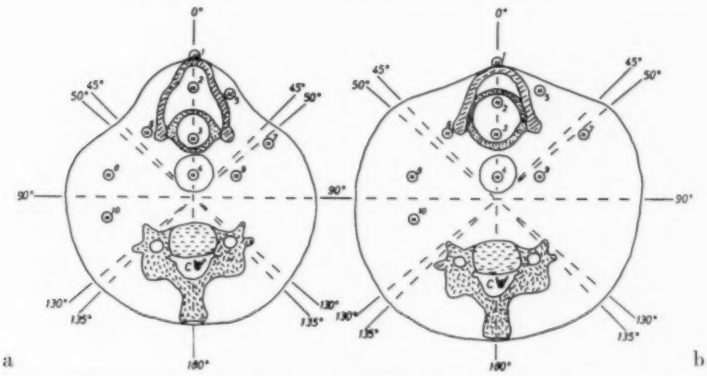

Abb. 2. Schnitt durch das Halsphantom in Höhe von CV. Es wurden die Messpunkte und die benutzten Pendelwinkel eingetragen.
a. ∅ = 11.7 cm. b. ∅ = 13.5 cm.

Für die PK ergaben sich folgende Verhältnisse: Am »dicken Hals« (13.5 cm ∅) gelten die Angaben der Tabellen in vollem Umfang; am »dünnen Hals« (11.7 cm ∅) musste der Drehpunkt bei einem Pendelwinkel von ± 45° gegenüber der errechneten Tiefe um 25 mm höher gelegt werden, um das Maximum in der gewünschten Tiefe (4 cm) zu haben. Bei grösseren Winkeln (180°, 240° und 280°) nahm die wirkliche Drehpunkttiefe gegenüber der errechneten relativ zu Tabelle 1).

Selbst unter Berücksichtigung des kürzesten Haut—Herd-Abstandes (Punkt 5 in Abb. 2) bei der Berechnung der Drehpunktverschiebung für die PK entsprechen die Messergebnisse hinsichtlich der Lage des Maximums nicht den Berechnungen nach der Tabelle. Diese Differenz beruht wahrscheinlich einmal auf der verminderten Strahlenabsorption durch die »Trachea« und zum anderen auf die gegenüber einem Wasserphantom veränderte Streustrahlung.

Dies erklärt auch, dass am »dicken Hals« nicht der kürzeste Haut—Herd-Abstand (5 in Abb. 3) sondern die Herdtiefe in der Winkelhalbierenden für die Berechnung der Drehpunktverschiebung massgeblich ist. Die Drehpunktverlagerung selbst erfolgt im vorliegenden Fall in der Winkelhalbierenden. Für die Berechnung der relativen Tiefendosis (rel. TD) bleibt jedoch der in Punkt 5 (s. Abb. 2 u. 3) gemessene Wert entscheidend.

11.7 cm — Halsphantom; 2.5 × 5 cm Herdfeld (Abb. 3 a). Bei allen drei Methoden ist die rel. TD bei einem Pendelwinkel von ± 140° am günstigsten, während die Bestrahlungszeit gegenüber den anderen Pendelwinkeln verlängert ist. Die Werte der Pendelbestrahlungen am TU 1 und am Pendelgerät nach KOHLER (P. n. K.) unterscheiden sich prak-

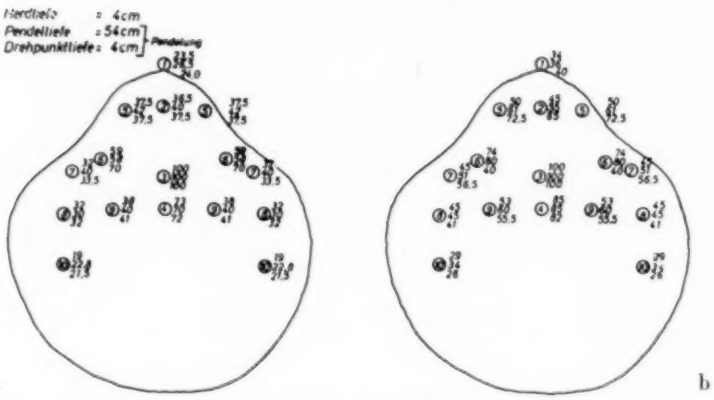

Abb. 3. Prozentuale Dosisverteilung in Höhe von CV für das Phantom des »dünnen Halses«. Bestrahlungsbedingungen: 200 kV; 20 mA; 0,5 mm Cu-Filter. Pendelwinkel = ± 140°. a. Feldgrösse: 2,5 × 5 cm. b. Feldgrösse: 3,5 × 7 cm.

tisch nicht, obwohl der grössere Fokus—Haut-Abstand (FHA) eine Verbesserung der rel. TD für das P. n. K. zur Folge haben sollte. Da die Translation infolge der ungünstigen topographischen Verhältnisse am Hals (Unterkiefer, Schultern!) nur in sehr beschränktem Masse ausgenutzt werden kann, bringt die PK keine nennenswerte Dosisverbesserungen; im ganzen gesehen wird jedoch das Herdfeld gegenüber der alleinigen Pendelung homogener, ohne dass die rel. TD verbessert würde (s. Abb. 3 a).

11,7 cm — Halsphantom, 3,5 × 7 cm Herdfeld (Abb. 3 b). Bei dem grösseren Feld ist die rel. TD der Pendelung mit dem P. n. K. wegen des grösseren FHA deutlich günstiger als beim TU 1. (Pendelung und PK.) Andererseits ist der Dosisabfall bei der PK seitlich und hinter dem Herd etwas steiler als bei der reinen Pendelung mit beiden Geräten. Der grösste Pendelwinkel (± 140°) hat sich auch bei der PK im Hinblick auf die Dosisverteilung am günstigsten gezeigt.

13,5 cm — Halsphantom, 2,5 × 5 cm Herdfeld (Abb. 4 a). Gegenüber den Messungen am »dünnen Hals« zeigen die Ergebnisse am »dicken Hals« für die Methoden beider Geräte eine noch weitergehendere Übereinstimmung. Dabei ist die rel. TD beim P. n. K. zahlenmässig am günstigsten (38,5, 42 bzw. 40 : 100), wobei die Differenz jedoch nicht gesichert werden kann. In der Umgebung des Herdes ist die Belastung und damit auch die Homogenität des Feldes bei den drei Methoden etwa gleich gross, während sie hinter dem Herd für die PK geringer wird.

13,5 cm — Halsphantom, 3,5 × 7 cm Herdfeld (Abb. 4 b). Wie bei dem Phantom mit dem kleineren Durchmesser findet sich wiederum die

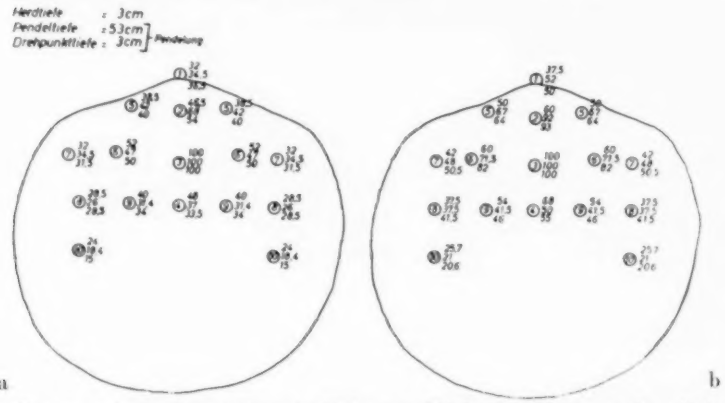

Abb. 4. Prozentuale Dosisverteilung in Höhe von CV für das Phantom des »dicken Halses«. Bestrahlungsbedingungen: s. Legende Abb. 3.
a. Feldgrösse: 2.5 × 5 cm. b. Feldgrösse: 3.5 × 7 cm.

günstigste rel. TD für das P. n. K. (50 : 100), während zwischen Pendelung und PK mit dem TU 1 (67 bzw. 64 : 100) kein deutlicher Unterschied besteht. Lateral vom Herdgebiet ist der Dosisabfall beim P. n. K. im Vergleich zur PK sehr steil. Die Werte hinter dem Herd liegen beim TU 1 niedriger; insgesamt erscheint das Herdfeld der PK homogener ausgelastet.

Die Messungen am Konvergenzstrahler wurden mit Hilfe der von FETZER entwickelten neuen Abstandstubusse durchgeführt, da die ursprünglich vorgesehenen Abstandstubusse eine exakte Einstellung am Hals weder sagittal noch seitlich zulassen.

Bei einem Vergleich der rel. TD bei Einstrahlung über ein mediales Feld zeigt sich, dass bei der Kombination: Abstandtubus 7, Herdfeldblende 6 diese etwa in Höhe der rel. TD eines 3.5 × 7 cm grossen Herdfeldes der anderen Methoden liegt, ohne dass das Maximum räumlich entsprechend gross oder homogen wäre.

Bei Einstrahlung über zwei seitliche, in einem bestimmten Winkel angeordneten Felder tritt keine Verbesserung der genannten Verhältnisse ein, da auch die vom Gegenfeld eingestrahlte Belastung zu beachten ist.

Besprechung der Ergebnisse

Die Messungen an Paraffin-Magnesiumoxyd-Halsphantomen (13.5 bzw. 11.7 cm ∅) haben ergeben, dass die Bewegungsbestrahlung des Larynx gegenüber der üblichen Stehfeldmethode Vorteile bietet. Insbesondere fand sich ein sehr günstiges Verhältnis zwischen Oberflächenbelastung und Herddosis, das bei dem kleinen Herdfeld (2.5 × 5 cm) besonders günstig ist (ca. 30—35 % der Herddosis).

Abgesehen vom Konvergenzstrahler, dessen rel. TD deutlich niedriger lag, erwiesen sich die verschiedenen Pendelmethoden und die Pendel-

Konvergenz praktisch als gleichwertig, obwohl bei Letzterer die Translation infolge der anatomischen Verhältnisse nicht in einem wünschenswerten, vorteilbringenden Mass ausgenutzt werden kann. Zwischen der Pendelung mit dem P. n. K. bzw. dem TU 1 besteht trotz des geringeren FHA am TU 1 hinsichtlich der Hautbelastung bei einem kleinen *Herdfeld* keine signifikante Differenz. Bei dem grösseren Herdfeld von 3.5 × 7 cm erwies sich dagegen der grössere FHA (P. n. K.) als günstiger. Werden jedoch bei der PK (TU 1) quadratische Felder (2.5 × 2.5 bzw. 3.5 × 3.5) benutzt, lässt sich trotz des kleinen Translationswinkels eine etwas günstigere Dosisverteilung gegenüber den rechteckigen Feldern erzielen.

Die rel. TD ist beim *Konvergenzstrahler* sowohl bei Einstrahlung der Dosis über ein wie auch über zwei Felder ungünstiger als bei den anderen Bewegungsbestrahlungsmethoden, ohne dass auch nur eine ähnliche Grösse und Homogenität des Maximums in Herdgebiet erreicht wird.

Als günstigster Pendelwinkel haben sich ± 140° herausgestellt, wobei am P. n. K. erst eine entsprechende technische Änderung vorgenommen werden musste. Die Einstellung selbst ist bei allen Geräten ohne besondere Schwierigkeiten möglich. Nur bei den seitlichen Konvergenz-Feldern ergeben sich im Hinblick auf das plane Aufsetzen des Tubus Schwierigkeiten, auf die auch schon FETZER (4) hingewiesen hat.

Bei der Einstellung haben sich im übrigen gegenüber den Angaben in den Tabellen einige Abweichungen herausgestellt, deren Ursachen im Einzelnen noch nicht vollständig geklärt werden konnten: Bei den *Pendelbestrahlungen* hat sich gezeigt, dass Drehpunkt und Maximum zusammenfallen. Bei der *Pendelkonvergenz* dagegen sind für den »dicken Hals« die Tabellenwerte bezogen auf die Herdtiefe in der Winkelhalbierenden massgeblich, für den »dünnen Hals« schälten sich jedoch eigene Verhältnisse heraus: Bei einem Pendelwinkel von ± 45° musste der Drehpunkt etwas höher gelegt werden als dem Tabellenwert, berechnet wie am »dicken Hals«, entspricht. Bei grösseren Winkeln (± 50°, 90, 120 u. 140°) bleibt der Drehpunkt am 11.7 cm-∅-Phantom in 4 cm Tiefe stehen, obwohl sich die errechneten Drehpunkttiefen-Werte allmählich der Herdtiefe nähern.

Auch am Konvergenzstrahler konnten wir eine »Verlagerung« des Maximums gegenüber dem in den Isodosentabellen angegebenen Wert nach unten feststellen; die Herdfeldblende musste daher entsprechend gewählt werden, um das Maximum zu heben.

Ohne Rücksicht auf den kürzesten Haut—Herd-Abstand folgt der Drehpunkt hinsichtlich seiner Tiefe eigenen Gesetzmässigkeiten.

Die u. U. erforderliche Verlagerung erfolgt den Vorschriften entsprechend in der Winkelhalbierenden.

Die Belastung der um den Kehlkopf herum und hinter dem Kehlkopf liegenden Weichteile ist, besonders bei der PK, nicht sehr hoch.

Die von uns gewonnenen Messergebnisse werfen erneut die Frage auf, ob es sinnvoll ist, bei der Bestrahlung des Larynx-Carcinoms Wege zu wählen, zu deren Durchführung noch zusätzliche Operationen wie z. B. die Stimmband-Freilegung bzw. die einseitige Schildknorpelentfernung notwendig sind. Gegenüber der bei einem derartigen Vorgehen angewandten weichen Strahlung bietet die harte Strahlung der Tiefentherapie auch biologisch gesehen Vorteile. Die Anwendung der Bewegungsbestrahlung bedeutet für den Patienten ein schonendes, bequemes therapeutisches Vorgehen, ohne dass darunter die Exaktheit der Bestrahlung (z. B. Einstellung, Dosis) leiden würde.

ZUSAMMENFASSUNG

Vergleichsmessungen an zwei Paraffin-Magnesiumoxyd-Halsphantomen (11.7 bzw. 13.5 cm ∅) ergeben, dass sowohl Pendelung (P. n. K., TU 1) als auch Pendelkonvergenz (TU 1) günstige Dosisverteilungen im Halsgebiet bei der Bestrahlung des Larynx zeigen. Es wird auf einige wichtige Gesichtspunkte bei der Einstellung des Drehpunktes bzw. der Pendeltiefe hingewiesen, die nicht den Angaben der beigegebenen Anleitungen entsprechen. Die günstigste Dosisverteilung ergab sich für die Pendelung wie für die Pendelkonvergenz bei einem Pendelwinkel von ± 140°. Die Filterung mit 0.5 mm Kupfer zeigte eine bessere relative Tiefendosis bei der Bewegungsbestrahlung als die mit 0.2 mm Kupfer.

SUMMARY

Comparative measurements on two neck phantoms of calcined magnesium paraffin (diameter 11.7 and 13.5 cm respectively) during irradiation of the larynx showed that a favourable dose distribution to the cervical region was obtained with pendular irradiation (P. n. K., TU 1) as well as with oscillatory convergent irradiation (TU 1). Some important observations on the adjustment of the pivoting point and the depth of convergency were made and found to deviate from the operation data. The most favourable dose distribution both for pendular irradiation and oscillatory convergent irradiation was obtained with an angular rotation of ± 140°. For moving field irradiation, filtration with 0.5 mm Cu gave a better relative depth dose than was obtained with 0.2 mm Cu.

RÉSUMÉ

Des mesures comparatives faites sur deux fantômes de cous en paraffine et oxyde de magnésium (11.7 et 13.5 cm de ∅) montrent que les mouvements pendulaire (P. n. K., TU I) et pendulaire convergent (TU I) donnent, dans l'irradiation du larynx, des distributions de dose convenables dans la région cervicale. L'auteur insiste, concernant la détermination du centre de rotation et de profondeur de convergence, sur quelques vues personelles importantes qui ne sont pas en accord avec les indications des instructions fournies avec l'appareil. C'est avec une amplitude d'oscillation de ± 140° que la distribution de dose la plus favorable a été obtenue pour le mouvement pendulaire et pendulaire convergent. En cinéthérapie, la filtration avec 0.5 mm de cuivre a donné une meilleure dose relative en profondeur qu'avec 0.2 mm de cuivre.

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BOOK REVIEWS

SEMEIOTICA NEURORADIOLOGICA. By Mario Lenzi. 320 pp., 400 figures, 5 tables. Editrice Cromotipia Ettore Sormani, Milano 1954.

The work is divided into two main parts: the skull with the brain, and the spinal cord. These two main parts are subdivided into chapters dealing with the techniques of the different kinds of examinations and elements of neuroradiologic diagnostics of tumorous or non-tumorous pathologic states.

The principal quality of the book resides in the clarity of presentation, a characteristic of all works published by this author. Among others, the chapters devoted to intracranial hypertension and to general considerations stand out as models. The reports on the techniques are preceded by carefully outlined anatomic summaries, always accompanied by suitable illustrations. The bibliographic documentation is also remarkably extensive, which makes the reading of certain chapters, for instance, the one on non-tumorous diseases of the brain, most agreeable.

These are the qualities that mould the book into a tome of general educational value, which should not be missing in the library of any physician of culture. However, since the book is also addressed to specialists, we feel it our duty to mention certain negative aspects.

In the treatment of the techniques of pneumographic examinations, the author produces plenty of details and illustrations concerning methods, in practice of rather limited usefulness. On the other hand, he has omitted to deal with principal developments, for example, he does not mention the modification of the encephalographic technique, the merit of which is due to LINDGREN and his school, and which consists in injecting air before commencing the evacuation of fluid, and in introducing more air than the quantity of fluid removed. Moreover, the author seems to be ignorant of works dealing with encephalography in cases of brain tumours, and he arbitrarily raises limits to the indications for this method, without substantiating his ideas by references to personal experiences.

In reading the chapters in the part dealing with tumours, especially cerebral tumours, the impression is gained that although the author is thoroughly familiar with the theoretical side, he is not very well acquainted with the practical problems such as they present themselves to the radiologist in his daily work in collaboration with the neurosurgeon. This is apparent from the fact that about a quarter of the illustrations (and more than one third in the chapter dealing with only the skull and the brain) emanate from borrowed material, and often from quarters which possess no neurosurgical centre.

These circumstances account for:

1. The inequality of the picture material.

2. The fact that the author is compelled to make use of negatives from special examinations to illustrate the normal or the pathologic states of the skull. In Fig. 189, p. 134, for example, a film from a ventriculography is displayed for exhibiting the morphology of the sella turcica, which, incidentally, is poorly shown; in Fig. 190, p. 135, a pneumographic examination serves to demonstrate the method of WASTINE and KINNEY for determining the position of the pineal body.

3. Insufficient information as to the verification of the cases. This matter gains in importance by reason of the fact that the captions supplied by the author for the illustrations often refer only to the definition of the disease, or else are explanations restricted to items of general character.

Let us take a few examples.

The captions for Figs. 243 and 244, pp. 174 and 175, indicate "deformation of the ventricles (ventricular deformation) from double haemorrhagic cyst in the oval centre".

The a. p. film shows, in fact, an asymmetric dilatation of the two ventricles and a slight displacement of the septum pellucidum. The lateral film reveals the ventricles asymmetrically dilated without significant deformation. In our opinion, it would have been of value in this case if the author had given not only his own interpretations of the films but had also indicated on what grounds these deformations permitted a diagnosis to be made.

The caption to Figs. 208 and 209, p. 153, reads "frontoparietal oligodendroglioma with small and fugitive residual image". In the first place, one would have liked to have known the grounds upon which the diagnosis of a fronto-parietal tumour was made. The films (lateral view only) show a displacement towards the base of the carotid siphon, a backward displacement and stretching of segment A2 of the anterior cerebral artery, and, possibly, a very diffuse zone of pathologic contrast (the reproductions are imperfect) immediately behind the anterior cerebral artery. No clear visualization of the middle cerebral artery is demonstrated, and no displacement of the pericallous artery or any pathologic vascularization in the parietal region is evident. One might sooner suspect the presence of a fronto-temporal tumour. Anyway, the arrows traced in Fig. 209 actually outline a fronto-temporal zone, where it is difficult to pass judgment on what had occurred. It is hard, also, to recognize the reasons for suspecting an oligodendroglioma, since a thin and diffuse residual contrast image is not usual with gliomas. It seems to us, therefore, that this case, if verified, should rather have been reported as exceptional.

The text for Figs. 125, 126, 127, 128, pp. 99 and 100 reads "osteoma of the frontal sinus with intracranial invasion; previous to the osteoma, a mucocele had been suspected from encephalographic and arteriographic findings". No indication is given for the reasons permitting a mucocele to be suspected by encephalography and arteriography. No filling of the ventricular system resulted from the encephalography. Arteriography (in the lateral plane only) shows only a probable backward displacement of the anterior cerebral artery.

As to Fig. 159, p. 116, one reads: "supra-chiasmatic meningioma, reactionary thickening of the spheno-chiasmatic plane; cisternal blocking and deformation". In our opinion, it would have been useful to indicate the kind of cisternal deformation arising in a case of supra-chiasmatic meningioma.

Fig. 251, p. 180, illustrates a case of tumour of the quadrigeminal bodies. The 'typical' deformation of the insufficiently filled posterior part of the 3rd ventricle, indicated by arrows, could in our view very well be associated with a pinealoma. If the case was verified, the question arises why the author has presented it without comments, since, from the ventriculographic point of view, it does not represent a typical illustration of a tumour of the quadrigeminal bodies. Likewise, for Fig. 252, p. 180, representing a case of ependymoma of the 4th ventricle, it would have been preferable if the author had accounted for the indications of an ependymoma and also had reproduced the other roentgenograms. Knowing the clinic from which this examination emanated, there is no need in this instance to be doubtful as to the verification of the case.

Finally, it seems to us that the author has been a little too free in offering conclusions of a general character, which may be taken seriously only if based on a writer's own firm statistics. One is at a complete loss to understand, for instance, why encephalography in cases of hematoma should be less valuable than ventriculography (p. 172) — on the contrary, the former is much more convenient as it permits the visualization of the sub-arachnoidal spaces, and, consequently, an estimation of a possible detachment of the brain from the vault; or the fact that in cases of metastases "the ventricles repel the air". A certain difficulty in filling the ventricular system may arise in all cases of tumours which produce very strong cerebral oedema but, at least in our experience, it seems to occur especially seldom with metastases.

Giovanni Ruggiero.

WELTRAUMSTRAHLUNG. DER HEUTIGE STAND DER BIOLOGISCHEN ERFORSCHUNG DER KOSMISCHEN STRAHLUNG IN GROSSEN HÖHEN UND IN ERDTIEFEN AUF GRUND NEUESTER UNTERSUCHUNGSMETHODEN. Von J. Eugster. 141 S., 46 Abb. Hans Huber, Bern 1955. Fr. 26.—.

The first part of the book gives a general survey of cosmic ray phenomena, especially of the heavy primaries, stars in nuclear emulsions due to spallations of nuclei by cosmic rays, and showers as examined with Geiger counters. Various chemical and biologic effects of the rays were investigated at heights up to 28,000 m (balloons being employed). Experiments of longer duration were conducted during the Swiss expedition to Mount Everest (8,000 m) and in the Swiss Alps (3,450 m). The effects of almost complete shielding from the cosmic rays were studied in the Simplon tunnel.

Of special interest is a method of exposing biologic objects, such as seeds and shrimp eggs, between nuclear plates. This affords the possibility, after the exposure, of selecting seeds or eggs which had been hit by heavy particles, either primary or secondary, recorded in the plates. The percentage of these objects showing evidence of biologic damage was much higher than among those not hit and among controls not exposed at all.

The last part of the book is devoted to the mutagenic and carcinogenic effects of cosmic rays. It does not appear possible as yet to say anything very definite about the importance these effects may have.

The work contains much useful and interesting information and deals with important questions; in addition it contains many excellent illustrations. It is all the more unfortunate that the text is written in such an unsystematic, incoherent manner as to make it most difficult for the reader to follow the arguments and himself form as clear a picture of the issues as the present available information permits. There are many minor as well as major errors, including references to illustrations not to be found in the book, and when the author refers to an illustration which actually appears or to a paper quoted, the reference numbers are not always correct. The proof-reading seems to have left a little to be desired.

Sven Benner.

ARTERIOGRAPHY OF THE UTERINE ARTERY. Its value in the diagnosis of uterine fibromyoma, tubal pregnancy, adnexal tumour, and placental site localization in cases of intra-uterine pregnancy. By Ingmar Fernström. 128 pp, 63 illustrations, 3 tables. Acta radiol. Suppl. 122, Stockholm 1955. Sw. Kr. 30: —.

The present work has been undertaken (1) to study the arteriographic findings in cases of fibromyoma, adnexal tumour, and of extra-uterine and intra-uterine pregnancy and, (2) to obtain an idea of the diagnostic value of the procedure. It is based on 450 gynecologic and obstetric cases examined by pelvic arteriography.

After giving a survey of the literature the technique used in pelvic arteriography is described. A description of the normal anatomy of the uterine artery then follows and is illustrated by numerous reproductions of drawings, radiographs of operation specimens after arterial injection, and arteriograms. Later chapters deal with the arteriographic appearances in uterine fibromyoma, adnexal tumour, as well as in extra-uterine and intra-uterine pregnancy. Each chapter is followed by reproductions of drawings, radiographs of operation specimens after arterial injection, and arteriograms showing characteristic arteriographic findings in these cases. In the concluding part of the book the value of pelvic arteriography in the diagnosis of uterine fibromyoma, tubal pregnancy, adnexal tumour, and placental site localization in cases of intra-uterine pregnancy, is discussed.

Autoreview.

STUDIES ON THE DISTRIBUTION AND FATE OF S^{35}-LABELLED BENZYLPENICILLIN IN THE BODY. By Sven Ullberg. 110 pp, 36 illustrations, 7 tables. Acta radiol. Suppl. 118, Stockholm 1955. Sw. Kr. 25: —.

The aim of this investigation was to study some of the pharmacologic properties of penicillin; how it is distributed from the blood to different body tissues and how it is bound, inactivated and excreted. In order that penicillin shall exert its antibacterial activity in the body it must come into contact with the pathogenic microbes and its concentration in the immediate vicinity of these must be sufficiently high. A careful study of the distribution pattern in both normal and pathologically changed tissues is therefore of therapeutic interest.

Biosynthetically prepared penicillin containing the radioisotope S^{35} has been prepared and its distribution studied with autoradiographic technique.

The culture and extraction methods employed in the preparation of S^{35}-labelled benzylpenicillin are described and general problems connected with the biosynthesis of radiopenicillin discussed.

The autoradiographic technique was adapted to the requirements imposed by the water solubility of penicillin and also to the desire to obtain survey pictures *e. g.* of whole mice. Experiences of freeze-drying technique compared to freeze-room sectioning are also discussed.

The varying density of large histologic survey sections of whole mice was investigated with quantitative betaradiography. This investigation formed the basis for calculation of self-absorption of the radiation from a section.

Survey autoradiographs illustrating the distribution of penicillin in adult mice at different times after intravenous injection are given.

Large survey autoradiographs of pregnant animals permitted studies of tracer distribution in the foetus and foetal fluids in the same picture as the mother.

Detail autoradiographs are shown illustrating the distribution of penicillin in regions of special clinical interest such as the brain, eye, sinuses of the skull, nasal conchae, teeth and paradental tissues, synovial cavities, skin, bone-marrow, mammary glands, and postparturiant uterus.

The autoradiographic investigation also provided possibilities of studying the different ways of excretion as well as the problem of accumulation in the organs.

Some autoradiographic observations were also made on the penetration of penicillin into abscesses and dry necroses. (In the cases investigated penicillin passed the abscess membrane but the further diffusion towards the centre of the abscess was very unsatisfactory in the chronic cases. The penicillin penetrated very poorly into dry necrotic areas.)

Geiger-Müller counter measurements were used to study the penetration of penicillin into blood and carcinoma cells, its binding to plasma proteins, and its volume of distribution in the body.

A paper electrophoretic investigation of urine from animals treated with radioactive penicillin showed the presence of two radioactive components. The major component had the same mobility as penicillin and was biologically active. The smaller component with a higher mobility was biologically inactive. Its rate of migration corresponded with that of S^{35}-penicilloic acid prepared in vitro by the inactivation of S^{35}-penicillin. The distribution of penicilloic acid in the body showed no obvious variations from the distribution of penicillin according to survey autoradiographs.

Autoreview.